VOLUME 62 *July 1950* NUMBER 1-B

THE AMERICAN REVIEW OF TUBERCULOSIS

OFFICIAL JOURNAL OF AMERICAN TRUDEAU SOCIETY
MEDICAL SECTION OF NATIONAL TUBERCULOSIS ASSOCIATION

BALDWIN MEMORIAL ISSUE

CONTENTS

Editorial 1
The Concept of Resistance to Tuberculosis. ESMOND R. LONG 3
Variations in Individual Susceptibility to Industrial Dusts Inhaled into the Lungs. ARTHUR J. VORWALD 13
Dissociation of the Tubercle Bacillus. A Review. WILLIAM STEENKEN, JR. 22
Inhibition of Growth of Tubercle Bacilli by Certain Vitamin Analogues. HILDA POPE AND DAVID T. SMITH 34
The Pathogenesis of Certain Forms of Extrapulmonary Tuberculosis. HUGH E. Burke 48
The Patient and the Physician. JAMES J. WARING 68
Rehabilitation from the Standpoint of the Tuberculosis Physician. STUART WILLIS 76
Bronchial Stenosis. EDGAR MAYER AND ISRAEL RAPPAPORT 80
Present Status of Therapeutic Pneumothorax. J. N. HAYES 90
Cardiac Symptoms in the Tuberculous Patient. DANIEL M. BRUMFIEL 98
Inauguration of the Edward L. Trudeau Foundation and The Trudeau School of Tuberculosis. ROY DAYTON 104
BIBLIOGRAPHY. EDWARD R. BALDWIN 114

Guest Editor
EDWARD N. PACKARD
Trudeau, New York

Published Monthly at Mount Royal and Guilford Avenues, Baltimore 2, Maryland by the National Tuberculosis Association • Business Off., 1790 Broadway, New York 19, N. Y.

Copyright 1950, by the National Tuberculosis Association

PRINTED IN U. S. A.

Part 2 of 2 Parts

THE AMERICAN REVIEW OF TUBERCULOSIS

OFFICIAL JOURNAL OF AMERICAN TRUDEAU SOCIETY

EDITOR-IN-CHIEF
ESMOND R. LONG
Philadelphia, Pa.

MANAGING EDITOR
WALSH McDERMOTT
New York, N. Y.

EDITORIAL BOARD

W. EDWARD CHAMBERLAIN, Philadelphia, Pa.
HALBERT L. DUNN, Washington, D. C.
H. CORWIN HINSHAW, San Francisco, Calif.
KIRBY S. HOWLETT, JR., Shelton, Conn.
JOHN C. JONES, Los Angeles, Calif.
ALEXANDER D. LANGMUIR, Baltimore, Md.
JOHN D. STEELE, Milwaukee, Wis.
WILLIAM B. TUCKER, Minneapolis, Minn.
ARTHUR J. VORWALD, Trudeau, N. Y.

HELEN W. MILLER
Editorial Secretary

NOTICE TO SUBSCRIBERS AND CONTRIBUTORS

THE AMERICAN REVIEW OF TUBERCULOSIS is published by the National Tuberculosis Association and issued monthly about the first of the month. THE AMERICAN REVIEW OF TUBERCULOSIS is the official journal of the American Trudeau Society. A volume includes six numbers and begins with the January and July numbers.

Subscription: The subscription price of the REVIEW is $10 for the calendar year. Checks should be made payable to Collier Platt, Treasurer.

Character of the Review: The REVIEW invites the submission of original manuscripts on any phase of tuberculosis, nontuberculous pulmonary diseases, and related subjects of interest.

MANUSCRIPTS

Contributors are requested to pay particular attention to the following rules governing the preparation of manuscripts. Failure to follow these rules is a frequent cause of delay in the publication of articles.

Manuscripts should be sent in duplicate to the office of the Managing Editor, Walsh McDermott, 1790 Broadway, New York 19, N. Y., mailed flat, and transmitted by first-class mail with postage for return if not acceptable. They should be in English, double-spaced, typewritten on one side of the page, with wide margins. Tabular data should not be included in the text but should be presented in separate tables with appropriate reference in the text. All case reports should be written in complete sentences. Authors should exercise particular care in the preparation, notation, and description of figures and tables. References should be in REVIEW style. Each table must be accompanied by a descriptive title, and a suitable legend must be provided for each figure. Drawings must be made with india ink and all lettering should be made with a stencil. The quality of the reproduction of a roentgenogram depends upon both the quality of the original picture and of the glossy print obtained from photographing that picture. If a contributor does not have facilities available, preparation of figures or reproduction of roentgenograms may be handled through the Review office. Under those circumstances, the contributor should supply a neat, properly proportioned, and suitably entitled drawing or the original roentgenogram, and will be expected to defray the cost of these services.

The publishers will not be responsible for manuscripts, illustrations, etc., lost in transit. In order to save expense for authors' corrections in proof, manuscript should be carefully revised by the author before submission.

Abstracts: Authors wishing to have abstracts of their papers appear in ABSTRACTS OF TUBERCULOSIS will facilitate their publication by sending concise abstracts or reprints to the Managing Editor.

Reprints: Fifty reprints without covers of articles will be furnished to authors free of charge when requested in advance. A table showing cost of additional reprints with an order blank is submitted with proofs to the authors.

Single Copies: The price of single copies of this number of THE AMERICAN REVIEW OF TUBERCULOSIS is one dollar postpaid.

Advertising: Rates will be furnished by THE AMERICAN REVIEW OF TUBERCULOSIS, 1790 Broadway, New York 19, N. Y. on request.

The Publishers reserve the right to decline any advertising submitted and to censor all copy. Acceptance of an advertisement does not constitute official endorsement of the product advertised.

Entered as second-class matter March 9, 1917, at the post office at Baltimore, Md., under the Act of August 24, 1912. Acceptance for mailing at special rate of postage provided for in section 1103, act of October 3, 1917. Authorized on July 2, 1918.

Editorial

EDWARD R. BALDWIN

This issue of THE AMERICAN REVIEW OF TUBERCULOSIS is dedicated to the memory of Dr. Edward R. Baldwin, former director of the Saranac Laboratory and the Edward L. Trudeau Foundation, and dean of the medical profession in the Saranac Lake area for many years. As a young physician with tuberculosis, he arrived in Saranac Lake in December 1892, and the succeeding years of his long life were spent in outstanding research in various phases of the disease from which he suffered. In collaboration with Dr. E. L. Trudeau he embarked upon extensive experiments with the then recently discovered tubercle bacillus. His achievements in this field are the foundation stones upon which is reared much of our knowledge of host susceptibility and host resistance. As Long says in his contribution to this issue, "In the development of concepts on the induction, nature, and practical importance of acquired resistance, few investigators have been more influential." With keen eyes he observed the effects of his experiments in animals, and his interpretation and deductions of the results were logical and often unassailable. He was sure of his ground and, although his stand on such subjects as native and acquired resistance in tuberculosis has been challenged, his fundamental concepts have not been discredited.

The search for truth through experimental research was his main object in life but he also practiced the art of medicine; indeed he was forced to do so in order to make a living, for he never received even a small salary from the Sanatorium and but little from the Foundation for his laboratory activities. This, however, was not an unmixed blessing for he was able to correlate the laboratory findings with the reactions of his patients to tuberculosis.

Doctor Baldwin was one of those rare individuals who excelled in the laboratory as well as in clinical medicine. But he recognized in later life that in the present world, with the enormous expansion of the laboratory fields and the great advances in medicine, one cannot grasp all the fundamentals and that the young man entering upon a career must choose either one or the other.

Doctor Baldwin's writings covered a multitude of subjects closely associated with the problems of tuberculosis. One has but to scan his bibliography to realize the extent of his interests and knowledge. Here are found articles on the building of sanatoriums; public health measures; advice to patients; climatology; clinical reports; "cures" for tuberculosis; and the many publications of the results of his laboratory researches, in which are included observations on the growth and cultural characteristics of the bacillus as well as analyses of its chemical components. He guided and counselled Petroff and his co-workers in the dissociation phenomena of the tubercle bacillus.

In 1918, in writing on "Research Problems in Tuberculosis," he discussed the relation of tuberculous infection to occupation and said: "Comparatively little is as yet known of the cause of the high death rate from tuberculosis in some dusty trades and experiments are needed to aid the solution of such questions." Under his stimulus, Gardner set up animal-dusting chambers to explore the effects of various inhaled inorganic dusts upon the course of pulmonary tuberculosis. From this beginning, and with the advice and encouragement of Dr. A. J. Lanza, the Trudeau Foundation extended its investigations and has made, and is making, its contribution to the solution of the problems of tuberculosis and of respiratory disability arising from the dusty trades.

In the following pages will be found contributions from a few of the many who worked with Doctor Baldwin and who were influenced by him. Here will be found a critique of his studies in resistance; a review of the story of dissociation of the bacillus; a study of one phase in the pathogenesis of tuberculosis; the variations in the reactions of the lungs to inhaled dusts; and other articles on the clinical and laboratory side of tuberculosis, subjects with which Doctor Baldwin was familiar through actual practice.

Doctor Baldwin was one of the founders and the first editor of THE AMERICAN REVIEW OF TUBERCULOSIS. He was instrumental in establishing the Trudeau School of Tuberculosis in 1916, which to the present day has enrolled over 800 students, 20 per cent of whom have come from twenty-nine foreign countries. Mr. Dayton in his contribution tells of these early days and of the beginnings of the Edward L. Trudeau Foundation.

The world of tuberculosis owes much to Doctor Baldwin. He built soundly and his influence is felt far and wide. A modest man, he sought neither fame nor riches. He "hewed to the line" and was not turned aside by the alluring fields of "cures" for tuberculosis. His experience, gained in the laboratory, pointed out the true paths and saved himself and others from following false leads.

Although in later years the infirmities of age caused his retirement from private practice and from the activities of the laboratory, he was mentally alert and remained a wise guide and counselor to the end. He died in May 1947, at the age of 83, honored and revered by all.

EDWARD N. PACKARD

THE AMERICAN REVIEW
OF
TUBERCULOSIS

VOLUME 62 *July 1950* NUMBER 1-B

THE CONCEPT OF RESISTANCE TO TUBERCULOSIS

With Special Reference to the Contributions of Edward R. Baldwin

ESMOND R. LONG[1]

The nature of resistance to tuberculosis has been a problem since the first recorded observations on the disease. Environment and the predisposing influence of inherent constitutional traits were stressed by the ancients. After the discovery of the tubercle bacillus, emphasis shifted from the role of native to that of acquired resistance. In the development of concepts on the induction, nature, and practical importance of acquired resistance, few investigators have been more influential than Edward R. Baldwin.

TRUDEAU, BALDWIN, AND KRAUSE AND THE SARANAC LAKE "SCHOOL"

In the development of understanding of resistance, American research was outstanding. E. L. Trudeau pioneered in this field as well as in the treatment of tuberculosis. His exacting professional duties, however, limited his activity as a laboratory investigator and it was fortunate indeed for Trudeau and tuberculosis research when one morning in December 1892 "a slender and pale young man" rang Trudeau's doorbell and "floored" him with the announcement that he had found tubercle bacilli in his sputum and knew he suffered from tuberculosis (1).

This matter-of-fact declaration by young Baldwin, at a time when the bacillus was hardly known in America, won Trudeau's instant respect. In a few weeks Baldwin's position as Trudeau's partner in research on the nature of tuberculosis was established. For thirty years he worked intensively in this specialized field.

For convenience of study, Baldwin's contributions may be grouped roughly by decades from 1900 to 1930. After 1930, when he was 66 years old, his duties were largely administrative, and his productivity as a scientific investigator had almost ceased.

As early as 1908 he was recognized as the American leader in the investigation of resistance to tuberculosis. He of all Americans was selected to present the subject at the Sixth International Congress on Tuberculosis, held in Washington, under the presidency of William H. Welch of Baltimore, September 21 to October 12, 1908. His paper, entitled "The Problem of Immunity in Tuber-

[1] Director, The Henry Phipps Institute of the University of Pennsylvania, Philadelphia, Pennsylvania.

culosis," was given before the Section on Pathology and Bacteriology. In addition to Welch, the honorary president of the Section, A. Calmette of Lille, and the honorary president of the Congress, Robert Koch of Berlin, were on the platform. Baldwin's paper (2) was based on an extraordinary familiarity with the literature in the field and his own investigations at Saranac Lake. He distinguished inherent from acquired resistance, and indicated his individual interest, and followed the trend of the times as well, in his emphasis on acquired resistance, citing the principle of immunization with bacteria of attenuated virulence, formulated by Pasteur and applied to tuberculosis after Koch's discovery of the bacillus, as the "common motif" of current research. He called attention to the pioneer American experiments of Dixon (1889), Trudeau (1892), de Schweinitz (1894), and Pearson and Gilliland (1902), all of which established that inoculation of small numbers of tubercle bacilli of low virulence for the selected animal host, e.g., human-type bacilli in cattle and avian-type bacilli in guinea pigs, raised the level of resistance to virulent infection. He stressed the fact that all investigations demonstrated the superiority of live bacilli over dead bacilli or bacillary preparations, such as Koch's T. R., but admitted that the transiency of heightened resistance, even with live bacilli, made the outlook discouraging for successful application of the principle for either man or cattle. He emphasized the need for further research on methods of vaccination, e.g., by feeding and inhalation, as well as injection. In explaining the mechanism of heightened resistance, he drew special attention to the hypersensitive state and the increased bacteriolytic power of tissue cells and their increased tolerance for the poisons of the bacillus as important.

The morning's papers, which included presentations by Calmette and Guérin of Lille, J. Bartel of Vienna, Courmont and Lesieur of Lyon, and Webb and Williams of Colorado Springs, were discussed by Koch and Trudeau, who agreed with Baldwin's concepts on the reality of acquired resistance and its limitations in practice.

A more comprehensive picture of Baldwin's views on the nature of resistance to tuberculosis in the opening decade of the century is given in his chapter entitled "Resistance, Predisposition and Immunity," in Arnold Klebs's *Tuberculosis*, an American classic (3), which opened with a scholarly historical sketch by William Osler and included as authors of individual chapters the leading American tuberculosis investigators of the time.

In this work Baldwin defined native and acquired factors in resistance. He outlined the normal physiological mechanisms by which the body wards off the entrance of tubercle bacilli, and emphasized apparent age, sex, and race differences in resistance. He pointed to the effect of long exposure of populations in eliminating the natively most susceptible stocks and thereby raising the average level of resistance. He noted the effect of certain diseases, e.g., diabetes, in depressing resistance, and the effect of trauma in creating a focus of lowered resistance. He expressed faith in a favorable influence of good nutrition and hygiene on native resistance, a concept for which he had some experimental evidence in the investigations of Trudeau.

Closer to his own interests, however, was the subject of acquired resistance.

The clinical observations of others and his own experiments had convinced him of the possibility of inducing "a high degree of *relative* immunity in tuberculosis" and raised the "hope for its future application in the prevention of tuberculous infection in the human race, a matter of transcendent interest and importance." He reiterated his conviction that, although preparations of dead bacilli did confer some degree of immunity, the greatest success could be obtained with living bacilli of low virulence—a view widely prevalent today, more than forty years later, and evident in the expanding program of BCG vaccination.

In attempting to elucidate the basis for heightened resistance, he stressed, more clearly than in previous publications, the important role played by enhanced activity of phagocytic cells and "tuberculin sensitivity." His own researches were now carrying him forward in the latter field (4).

In each decade a personal association was of great importance in the development of Baldwin's ideas. In the first ten years of the century Trudeau stimulated Baldwin. In the second, Baldwin stimulated the interest and developed the opportunities of Allen K. Krause (5, 6), who soon became the spokesman for the Saranac Lake school of thought on tuberculosis and surpassed all his predecessors and associates in literary output and didactic statement. At the opening of this period important investigations abroad had laid a path for further research. The pioneer work of von Pirquet on tuberculin and its direct application by P. Römer (7) to the theory of immunity, profoundly influenced Krause and had a formative influence on the course of Baldwin's research. At the end of the second decade and throughout the third, Baldwin cooperated with a new student, Leroy U. Gardner, and later yielded his own position to him.

By this time the Saranac Lake line of thought was being pursued in a dozen places (8). A monumental paper by Baldwin and Gardner (9) on "Reinfection Tuberculosis" recounted their own experience on the effect of first tuberculous infection upon the course of a subsequent infection, and marshaled an impressive array of evidence from the work of the rest of the world for the concepts of "primary" and "reinfection" tuberculosis, and the effect of the one on the course and character of the other. The evidence cited had immediate bearing on the problem of endogenous and exogenous infection as the cause of chronic pulmonary tuberculosis. The authors left the question unsettled, although inclining to the view that cumulative infection in childhood was the basis of phthisis in the adult, i.e., in effect, that reinfection tuberculosis of later years was predominantly endogenous. "The main fact of universal infection, single or repeated" before adult years, supported, as it was, by thousands of tuberculin tests and necropsies, was accepted by Baldwin and Gardner as the factor responsible for the characteristic features of adult tuberculosis, the authors stating unequivocally that "in comparison with the ease with which a primary infection is acquired the later inhaled and ingested bacilli are resisted more or less strongly by the 'relative immunity from infection'."

A fundamental concept for the control of tuberculosis, combining a statement of the importance of both native and acquired resistance, was laid down: "Good physiological functions, combined with the immunity from infection, tend to ward off further infection after adult age is reached. Should the conditions be

otherwise than favorable, or the infection frequent or potent, disease results."

Essentially no change occurred in Baldwin's expressed views after this date (1921). His last significant contributions on the subject of resistance were chapters quite evidently from his hand in the well-known volume *Tuberculosis: Bacteriology, Pathology and Laboratory Diagnosis* by Baldwin, S. A. Petroff, and L. U. Gardner (10). The role of hypersensitivity in heightening inflammatory reactivity to tubercle bacilli, whether the latter were of endogenous or exogenous source, was stressed more vigorously than six years before, and the importance of cells rather than body fluids in the defense of the host was emphasized strongly. "The inference is fair," one statement reads, "that the . . . epithelioid cells . . . have acquired a specific digestive power, which is quickly brought into action by the presence of such products of the bacilli as are soluble." In the same chapter a concept was included which through the advocacy of Baldwin and Krause had already had a far-reaching effect, not only on physicians and investigators, but on lay workers in the antituberculosis campaign as well, viz., a sharp distinction between "tuberculous infection" and "tuberculous disease," which was popularized by the National Tuberculosis Association and particularly by its Director of Publication and Extension, Philip P. Jacobs (11). The great frequency of tuberculous infection, established by tuberculin surveys, was looked upon as an important element in the resistance of populations to the development of progressive tuberculosis. In Baldwin's view, which was reiterated and developed in a long series of brilliant expositions and forceful pronouncements by Krause on the nature of resistance to tuberculosis, "breaks" in the widely prevalent "immunity of infection" opened the way for the development of clinical disease. A variety of physiologic strains were considered as possible initiating factors in these breaks.

That Baldwin drew much of his conviction from the deductive reasoning of Krause there can be no question. Krause, in turn, gave a high place to Baldwin's laboratory research in the formulation of his own concepts. Both based many of their conclusions on an extensive group of investigations by other members of the "Saranac Lake School."

In the late nineteen twenties their views were dominant on the nature of acquired resistance to tuberculosis. Their hypothesis, developed by Römer, elaborated by Baldwin, and widely and convincingly taught by Krause, recognized tuberculin allergy, i.e., the hypersensitivity of tuberculous infection, as the mechanism principally responsible for the enhanced resistance of the infected animal to new infection or progress of the old. The intensity of the allergic inflammatory response was considered the immediate cause of the heightened defensive action, and it was recognized that this response might be, in the words of Krause, a two-edged sword leading to destructive effects on tissue when the dose of reinfecting bacilli was large.

CURRENT CONCEPTS ON RESISTANCE

In 1929 the Baldwin-Krause view was sharply challenged by Arnold Rich and H. A. McCordock (12). At a time when "it was a major heresy to question the importance of hypersensitivity," Rich called attention to a number of factors

that did not fit with the current dogma. First was the fact that tuberculosis may pursue a strikingly unfavorable course in persons, particularly Negroes, highly sensitive to tuberculin. Secondly, a series of carefully conducted animal experiments by himself and his associates convinced him, on the other hand, that a heightened acquired resistance could be developed and maintained in the absence of tuberculin sensitivity, the latter being either abolished or prevented in its development by massive and repeated injection of tuberculin. Rich and McKee (13) noted that, when the hypersensitivity of infection was abolished by any means, the greatly reduced inflammatory response to infection still sufficed to keep a new infection well checked, as compared with the course of a similar infection in a nonimmunized animal.

In summary, Rich concluded that immunity and the hypersensitivity of infection are not necessarily related, that experimentally the one can be readily dissociated from the other, and that immunity may be more effective in the absence of the hypersensitivity of infection than in its presence. He took pains to point out, however, in a later extensive review of the whole subject (14) that hypersensitivity is not always deleterious and that it may under certain circumstances be a useful auxiliary in the machinery of resistance.

The exact mechanism of acquired resistance, he admitted, remained a puzzle. Whatever its innate nature, the effect was a restriction of the ability of tubercle bacilli in tissue to increase in number. The best evidence indicated that the mechanism was essentially cellular.

Rich's results and conclusions raised a controversy that has not yet subsided. Evidence accumulated against and for his views. Krause's colleague H. S. Willis (15) presented evidence indicating that hypersensitivity might be an important factor in the resistance even of immunized animals in which hypersensitivity had reached a very low ebb with the passage of time, for in such animals experiment showed that sensitivity returned rapidly on reinfection. Willis and his associates (16) showed also that desensitized guinea pigs on reinfection often developed lesions in which tubercle bacilli grew freely. Pinner (17) and others suggested that the apparently superior resistance of Rich's desensitized animals might be the result of natural selection in favor of resistance, rather than mere desensitization, since in the process of desensitization many animals died, leaving only the hardiest for comparison with the hypersensitive animals. On the other side of the question, studies by W. Pagel (18) indicated that hypersensitivity is the essential predisposing factor responsible for liquefaction of caseous tissue in the presence of large numbers of tubercle bacilli. The studies of Long, Holley, and Vorwald (19, 20) showed that in animals known to be refractory to the development of tuberculosis the inflammatory response to small inocula of tubercle bacilli was minimal, and that resistance, as shown by the failure of development and spread of tuberculous lesions, was in no way correlated with the development of hypersensitivity. In other words, whether acquired resistance was or was not associated with an accelerated and intensified inflammatory response to infection, the native immunity exhibited by animal species refractory to tuberculosis was not.

Within recent years renewed emphasis has been laid on native resistance and

its relation to acquired resistance. M. B. Lurie (21) has shown that strains of rabbits of greatly varying native resistance to tuberculosis may be propagated over long periods by close inbreeding, with maintenance of their original level of resistance. An important difference in behavior of the most widely divergent strains was the ability of the resistant and inability of the susceptible strains to localize the infecting bacilli at the point of entry, e.g., the lung or skin. In this respect the resistant rabbits behaved like vaccinated animals. It was noteworthy that the distinction between native and acquired resistance in the "natively" resistant animals was not sharp, for in the latter after infection a more rapid restriction of multiplication of tubercle bacilli occurred than in the susceptible animals (22); a fact which suggested that in the resistant animals native resistance represented in some measure at least an accelerated capacity for developing acquired resistance. This concept was fortified, from the point of view of those stressing the defensive character of hypersensitivity, by the fact that in many instances, if not as a rule, the capacity to react to tuberculin developed more rapidly and the reaction was more intense than in the susceptible animals. Another important observation was that the enhanced capacity to resist invasion by tubercle bacilli was not wholly cellular. Appropriate experiments showed that the body fluids of the resistant animal were concerned also.

Lurie's (23, 24, 25) latest experiments have led him to believe that hormonal influences are important in the defensive mechanism through their effect on tissue permeability and the mobilization and utilization of cellular elements. Experiments with sex hormones and other agents affecting the adrenal glands strongly suggest to him that hyperactivity of the adrenals favors resistance.

A relatively simple measure for resistance has been found by Lurie and Zappasodi (26) in the intracutaneous injection of BCG. In rabbits of resistant strains the lesion at the site of inoculation grows rapidly, reaches a peak quickly, and heals promptly. In susceptible rabbits the lesion grows and reaches its peak more slowly and heals much more tardily. Associated with the rapid reaction of the resistant animals a more rapid development of tuberculin sensitivity occurs, as a rule, and the reaction is generally more intense than in animals of susceptible stocks. Lurie believes that the prompt initial reaction in the resistant animals destroys bacilli rapidly with release of sensitizing antigens. Fundamentally the inflammatory reaction in natively resistant animals is like the reaction in immunized tuberculin-sensitive animals.

In commenting on the investigations of Lurie, Pinner (17) stressed the fact just cited, and designated, as the fundamental mechanism of resistance (whether native or acquired), localization of tubercle bacilli at the point of entry. In reading the opinions of different authors in the United States and abroad one finds rather general agreement on this point. Space will not be taken to cite other opinions. The analyses by Rich, Pinner, and Lurie, which may be considered as broadly representative, indicate that absolute agreement is unlikely. Each has been able to point out certain inconsistencies in the arguments of the others. Rich (14) therefore concludes that a middle position is probably closest to the the truth.

We are left thus with a concept of resistance that includes native and acquired resistance, and recognizes the fact that native resistance is in part a manifestation of rapidly developing acquired resistance. In either type prompt localization of invading bacilli at the point of entry is a significant element. The concept must also include recognition of the fact that in the highest levels of native resistance bacilli are quite unable to multiply, and inflammatory response is very slight. It is perhaps not far-fetched to compare this inhibition with that occurring when tubercle bacilli are exposed in a good culture medium *in vitro* to the action of a suppressing antibiotic.

OTHER FACTORS CORRELATED WITH NATIVE RESISTANCE

Before leaving the subject of native resistance, it seems not out of place to discuss a few other factors of supposed, although ill-defined, importance in resistance, including nutrition and psychic elements.

Good nutrition traditionally favors resistance. Valid evidence for the concept is, however, scanty. Observations on man are subject to numerous complications induced by environmental factors other than nutrition. For present purposes our attention is best confined to animal experiments. Such studies as have been made (27) indicate that protein, ascorbic acid, and vitamin A favor resistance. Experiments on mineral nutrition are equivocal. A recently reported study (28) indicates that the favorable action of protein may be in part indirect, since in the experiment described, carried out on rats, a suppressive effect of a high protein diet on intercurrent pneumonia, which is known to favor the spread of tuberculosis, was noted. Since there is little to controvert the idea that good nutrition favors resistance, and since many well-analyzed observations in man and a few well-controlled studies in animals support the view, it seems reasonable to believe that optimum nutrition helps to maintain good resistance. There is good scientific evidence that this may be so, for the conclusion is fortified by Cannon's (29) experiments on the relation of nutrition, particularly protein nutrition, to the production of antibodies.

The propriety of including psychic factors in a discussion of the fundamental elements of resistance may be questioned. In the mechanistic nineteen twenties and thirties moral and spiritual attributes, such as will power, persistence, stamina, and courage, while looked upon as laudable qualities in some vague way helpful in the individual fight against tuberculosis, were considered intangible, remote, and not susceptible to scientific evaluation in relation to resistance. Modern phthisiology is willing to take a more receptive view. Numerous articles on the psychologic attitude of tuberculous patients have appeared, and at least one promising start on the relation of psychiatric pattern to the prognosis of tuberculosis (30) has been made, suggesting that the attitude of the patient, however it may be mediated physiologically, is highly important. In the light of the current studies of Lurie and others on hormonal balance in relation to resistance, and the well-established influence of mental and emotional states on the balance of endocrine secretions, an indirect but none the less definite influence of mental states on resistance to tuberculosis in man is a real possibility.

Of other factors generally accepted as favoring resistance little can be said. "Fresh" air, in the sense of outdoor air, is much less in vogue than formerly, and no untoward effect on the course of tuberculosis is evident. There is general agreement, on the other hand, on the importance of rest and ill effect of overexertion, but rest and exercise clearly may affect the progress of tuberculosis in many nonspecific ways, and no satisfactory studies are available to form justified opinions on the effect of rest and excessive exercise alone.

CONCLUSIONS

With the most recently acquired facts before us and with the perspective of twenty years on the views of Baldwin and Krause, we may form an opinion of their contribution to the theory of resistance to tuberculosis. No fault can be found with the facts they discovered, and, although their conclusions have been contested in the light of subsequent experiments, their views have not been disproved. Baldwin's early distinction between inherent and acquired resistance is routinely taught, as in his time. Currently, emphasis has shifted from the latter to the former, and quite logically so, since an increasingly large percentage of adult chronic pulmonary tuberculosis develops from a primary lung infection. Under natural conditions, however, in this form of tuberculosis, hypersensitivity of infection, although absent at the outset when native resistance alone can play a role, is present within a few weeks, so that most of the course of the disease, whether favorable or unfavorable, is passed within the presence of hypersensitiveness. Therefore, the important facts learned by Baldwin on the relation of hypersensitivity to resistance and the defensive reaction of inflammation cannot be ignored in analyzing the pathogenesis of tuberculosis in its most characteristic forms today.

CONCLUSIONES

El Concepto de Resistencia a la Tuberculosis, con Referencia Particular a los Aportes de Edward R. Baldwin

Teniendo ante nosotros los datos más recientes y con una perspectiva de veinte años para las opiniones expresadas por Baldwin y Krauss, ya podemos formar juicio del aporte de esos autores a la teoría de resistencia a la tuberculosis. No puede encontrarse falta con los hechos que descubrieron, y, aunque se han disputado sus conclusiones a la luz de experimentos subsiguientes, no se han refutado sus ideas. La distinción temprana de Baldwin entre resistencia inherente y adquirida se enseña hoy día sistemáticamente, como en su época. Actualmente, se hace hincapié en la primera en vez de la segunda, y con bastante lógica esto, dado que un porcentaje cada vez mayor de tuberculosis pulmonar crónica en el adulto procede de una infección pulmonar primaria. No obstante, en las condiciones naturales, en esa forma de tuberculosis, la hipersensibilidad a la infección, aunque ausente al principio, cuando sólo la resistencia natural puede desempeñar un papel, se presenta en término de pocas semanas, de modo que la mayor parte de la evolución de la enfermedad, ya favorable o no, transcurre en presencia de hipersensibilidad. Por eso, al analizar la patogenia de la

tuberculosis en sus formas más típicas hoy día, no pueden pasarse por alto los importantes hechos averiguados por Baldwin acerca de la relación de la hipersensibilidad con la resistencia y la reacción defensiva de la inflammación.

REFERENCES

(1) Trudeau, E. L.: An Autobiography, New York, Doubleday Page and Company, 1916.

(2) Baldwin, E. R.: The problem of immunity in tuberculosis, Transactions of the Sixth International Congress on Tuberculosis, 1908, *1*, Part 1, 174; Am. J. M. Sc., 1909, *137*, 103.

(3) Baldwin, E. R.: Resistance, predisposition and immunity, *Tuberculosis*, Klebs, A. C., New York, D. Appleton and Company, 1909, Chapter III, p. 80.

(4) Baldwin, E. R.: Studies in immunity to tuberculosis: I. (a) Hypersusceptibility or anaphylaxis, J. Med. Research, 1910, *22*, 189.

(5) Krause, A. K.: Environment and Resistance in Tuberculosis, Baltimore, Williams & Wilkins Company, 1923.

(6) Krause, A. K.: Summary, analysis and applications of the studies on tuberculosis infection, Am. Rev. Tuberc., 1926, *14*, 271.

(7) Römer, P. H.: Spezifische Überempfindlichkeit und Tuberkuloseimmunität, Beitr. z. Klin. Tuberk., 1908, *11*, 79.

(8) Dayton, R.: Inauguration of the Edward L. Trudeau Foundation and the Trudeau School of Tuberculosis, Am. Rev. Tuberc., 1950, *62*, Part 2, 104.

(9) Baldwin, E. R., and Gardner, L. U.: Reinfection in tuberculosis. Experimental arrested tuberculosis and subsequent infections, Am. Rev. Tuberc., 1921, *5*, 429.

(10) Baldwin, E. R., Petroff, S. A., and Gardner, L. U.: Tuberculosis: Bacteriology, Pathology and Laboratory Diagnosis, Philadelphia, Lea and Febiger, 1927.

(11) Jacobs, P. P.: The Control of Tuberculosis in the United States, New York, National Tuberculosis Association, 1932.

(12) Rich, A. R., and McCordock, H. A.: An enquiry concerning the role of allergy, immunity and other factors of importance in the pathogenesis of human tuberculosis, Bull. Johns Hopkins Hosp., 1929, *44*, 273.

(13) Rich, A. R., and McKee, C. M.: A study of the character and degree of protection afforded by the immune state independently of the leucocytes, Bull. Johns Hopkins Hosp., 1934, *54*, 277.

(14) Rich, A. R.: The Pathogenesis of Tuberculosis, Springfield, Illinois, Charles C Thomas, 1944.

(15) Willis, H. S.: The waning of cutaneous hypersensitiveness to tuberculin and the relation of tuberculoimmunity to tuberculoallergy, Am. Rev. Tuberc., 1928, *17*, 240.

(16) Willis, H. S., Woodruff, C. E., Kelly, R. G., and Voldrich, M.: Allergic and desensitized guinea pigs. A study of factors bearing upon the problem of immunity in tuberculosis, Am. Rev. Tuberc., 1938, *38*, 10.

(17) Pinner, M.: Pulmonary Tuberculosis in the Adult, Springfield, Illinois, Charles C Thomas, 1945.

(18) Pagel, W.: Studies über tuberkulöse Erweichung, Beitr. z. Klin. Tuberk., 1931, *76*, 414.

(19) Long, E. R., Holley, S. W., and Vorwald, A. J.: A comparison of the cellular reaction in experimental tuberculosis of the cornea in animals of varying resistance, Am. J. Path., 1933, *9*, 329.

(20) Vorwald, A. J.: A comparison of tissue reaction to pulmonary infection with tubercle bacilli in animals of varying resistance, Am. Rev. Tuberc., 1933, *27*, 270.

(21) Lurie, M. B.: Heredity, constitution and tuberculosis: An experimental study, Supplement to Am. Rev. Tuberc., 1944, *44*, 1.

(22) Lurie, M. B., Abramson, S., and Heppleston, A. G.: Varying genetic resistance of

rabbits to quantitative inhalation of tubercle bacilli, Federation Proc., 1949, *8*, 361.

(23) LURIE, M. B., ABRAMSON, S., AND ALLISON, M. J.: The effect of estrogen and chorionic gonadotropin on the course of tuberculosis in highly inbred rabbits, Am. Rev. Tubere., 1949, *59*, 168.

(24) LURIE, M. B., HARRIS, T. N., ABRAMSON, S., AND ALLISON, M. J.: The effect of estrogen on skin sensitivity and on the allergy of the internal tissues, Am. Rev. Tubere., 1949, *59*, 186.

(25) LURIE, M. B., ABRAMSON, S., HEPPLESTON, A. G., AND ALLISON, M. J.: On the mode of action of estrogen and gonadotropin on the progress of tuberculosis, Am. Rev. Tubere., 1949, *59*, 198.

(26) LURIE, M. B., AND ZAPPASODI, P.: The response to BCG as an index of genetic resistance to tuberculosis, Federation Proc., 1950, *9* (Abstract in press).

(27) LONG, E. R.: Constitution and related factors in resistance to tuberculosis, Arch. Path., 1941, *32*, 122, 286.

(28) KOERNER, T. A., GETZ, H. R., AND LONG, E. R.: Experimental studies on the role of protein in resistance to tuberculosis, Proc. Soc. Exper. Biol. & Med., 1949, *71*, 154.

(29) CANNON, P. R.: Some pathologic consequences of protein and amino acid deficiencies, J.A.M.A., 1945, *128*, 360.

(30) LYON, J. M.: A study of psychic influences in minimal pulmonary tuberculosis, appended to WARING, J. J., AND ROPER, W. H.: Final report, section for research on minimal tuberculosis of the University of Colorado Medical Center at Fitzsimons General Hospital, submitted to U. S. Army Medical Research and Development Board and Subcommittee on Tuberculosis, Division of Medical Sciences, National Research Council, October, 1949 (Restricted. Formal manuscript of this report to be prepared for medical publication).

VARIATIONS IN INDIVIDUAL SUSCEPTIBILITY TO INDUSTRIAL DUSTS INHALED INTO THE LUNGS

ARTHUR J. VORWALD[1]

INTRODUCTION

Experience in examining large groups of human beings and experimental animals exposed to industrial dusts regularly demonstrates some basic principles for the guidance of all students of pneumoconiosis. The principles may be stated as follows:

1. Not all dusts are capable of producing pulmonary damage when inhaled into the lung.
2. Only a minor portion of all persons exposed to toxic dust develop pulmonary disease.

In a sense, these two principles are interrelated because if a specific dust, per se, is not capable of producing pulmonary damage, none of the exposed persons will develop pulmonary dust disease.

The essential factors governing the stimulation of the tissue response to an inhaled dust are related to chemical and physical characteristics of the dust, namely, to the composition and particle size. There are also other important determinants such as the concentration of particles in the atmosphere breathed by the subject and the duration of exposure of that subject. Nevertheless, there is also sufficient clinical evidence to support the view that not all persons exposed to a presumably hazardous concentration of toxic dust will develop pulmonary disease. This view is confirmed also by experimentation with animals. Thus, it appears that certain factors inherent in the host are responsible for the variations in individual susceptibility of men and of animals in their reaction to inhaled dust.

An attempt is made here to analyze those variations and to explain the comparative resistance of one individual to a toxic dust as opposed to the susceptibility of another individual under identical conditions of exposure. The explanation for this variation in reaction is of great theoretical and practical interest, for, if it could be shown that certain persons are actually resistant, the cause might be discovered and used as a basis for the selection of workers for industries with a dust hazard.

VARIATIONS IN MAN

It is pertinent to examine the evidence of individual variation as it relates to a dust of proved toxicity, such as quartz. There can be no doubt that quartz on inhalation into the lung is capable of producing a specific pulmonary disease, silicosis. Nevertheless, even with the high concentrations of quartz that existed in many industries before the present era of dust prevention, usually only a minority of all the exposed workers developed disease. Classification of workers

[1] Director, The Edward L. Trudeau Foundation and The Saranac Laboratory.

by duration of exposure shows increasing frequencies of pulmonary change with each successive five-year period of employment. This observation has led many investigators to conclude that given a sufficient period of exposure to quartz dust, everyone would ultimately develop silicosis. This conceivably could be true for industries that generate excessive quantities of dust of very high free-silica content, but such a viewpoint lacks statistical confirmation. In practically all well-studied industries there has been an appreciable group of men, employed for prolonged periods, whose lungs by roentgenographic examination have shown either no trace of abnormality or, at most, only nonspecific linear exaggerations which could not be identified as presilicotic.

Environmental factors: The most widely accepted view of individual variation of reaction to inhaled dust is that environmental factors combine in some unexplained manner to permit one individual to inhale more silica than do others in the same industrial environment. We know that the presence of certain minerals like calcined gypsum, when mixed with quartz, tends to reduce the amount of silica in the atmospheric dust. We know that local ventilation modifies the total concentration of atmospheric dust in different parts of the same workplace. Just how these and other chance environmental factors may combine to protect some, but not all, individuals employed in the same plant for twenty-five years or more is indeed puzzling.

Filtration by upper respiratory tract: It seems more likely that the protective factors involve the worker rather than his environment. Lehman (1) was impressed with this probability, and devised a method for testing the comparative efficiency of the nasal cavities in excluding dust from the lungs. By an elaborate method he was able to demonstrate that nasal filtration was much less efficient in those members of a group who developed silicosis than in other members similarly exposed who failed to develop the disease. This finding is difficult to interpret since silicosis is due to the inhalation of very fine dust particles which pass the nose freely and are deposited in the lungs. Numerous investigators (2–13) have demonstrated that, in general, the nose filters out of the inspired air particles greater than ten microns in diameter and that the bronchial tree is an effective barrier for particles above five microns. Only particles less than five microns gain access to the alveoli and are retained in sufficient quantity to produce pulmonary disease. Thus, it appears that differences in native effectiveness of filtration by the upper respiratory tract may explain variations in susceptibility among workers. This concept lacks confirmation since such differences have not been demonstrated, at least in sufficient degree to be detected in individuals with healthy tracheobronchial trees.

Physiologic peculiarities of the lung: A second possibility which has received consideration as a cause for variation in response relates to physiologic peculiarities of the lung itself. For example, variations as high as 10 to 15 per cent exist in the ventilatory function of healthy men as a matter of constitutional differences. The amount of air reaching the alveoli during the effort of work is much greater in some individuals than in others. Certain influences such as exercise, altitude, and excess carbon dioxide promote deep inspiration, and alveolar reten-

tion is enhanced by deep breathing (12, 13). Whether these physiologic differences may be responsible for the variable response to the dust is debatable. It seems clear, however, that the individual who breathes more air will inhale more dust and will be susceptible to more dust accumulation in the lung under the same conditions of exposure. It is also established that previous or simultaneous exposure to other substances may alter the physiologic response to inhaled dust such as silica. The bituminous coal miner who has received no apparent injury from prolonged contact with coal dust nevertheless reacts quite differently to a subsequent silica exposure than does the individual who had not previously been employed in a dusty trade. Similarly, the iron-ore miner reacts differently to a mixture of iron oxide plus quartz than to quartz alone. Another pertinent example is the finding that the presence of aluminum dust in the lung may protect that organ against the development of silicosis. Whether the presence of these substances in the lung alters the tissue response to toxic dusts, such as free silica, by a purely physicochemical mechanism, or whether they affect also the physiologic mechanism by which the tissues of the body handle the inhaled dust, is not clear. It would seem, however, that both mechanisms play a role.

Chronic infection: A third possibility relates to chronic infection of the respiratory tract. Here is a variable factor that by chance involves only a few members of any group. Chronic tracheitis and chronic bronchitis with bronchiectasis and bronchiolectasis may act by decreasing the efficiency of the protective mechanisms which remove dust from the inhaled air before it passes into the lung. Furthermore, these impairments tend to diminish the ability of the lung to rid itself of foreign material by way of the tracheobronchial tree. Consequently, more dust may reach the lung and be retained in the alveoli of some individuals than in the alveoli of others. But clinical, post-mortem, and experimental studies of lungs from subjects exposed to a great variety of dusts fail to demonstrate the presence of such impairments. In this connection greater attention has been directed to associated infection of the parenchyma of the lung. It is obvious that tuberculosis should be seriously incriminated since it is a concomitant of many cases of silicosis with disability, as has been demonstrated clinically and at autopsy. As greater experience is acquired in the interpretation of roentgenograms, however, it becomes apparent that the factor of tuberculous infection is more frequently a late complication supervening after the silicosis has been well established. In addition, clinical and experimental studies have demonstrated that it is possible for silicotic fibrosis to develop in the absence of tuberculosis or other infection of the lung. For these reasons the factor of infec tion as the major cause of variation in response has been minimized by most observers.

Lymphatic drainage: A fourth possible determinant of individual susceptibility to silica is the relative competence of the lymphatic drainage system in different individuals. All persons exposed to a given concentration of dust might conceivably inhale comparable quantities of dust, but it would tend to remain localized in the lung in those individuals whose lymph channels and nodes were obstructed by some residuum of previous injury. Pulmonary scars of healed infection in

persons exposed to dust retain more dust than do other areas of the organs. In the case of the familiar linear scars of healed tuberculosis, it is usually quite clear that there is a causal relationship between the entrapped dust, the fibrosis, and the blocked lymphatics at the site. The influence of pre-existing scar tissue in localizing inhaled dust has been demonstrated in the Saranac Laboratory by electrocauterization of lungs of animals some weeks before they were exposed to dust.

Autopsy material: Human autopsy material, analyzed by techniques of pathology and chemistry, should yield valuable information if accompanied by reliable data on the industrial exposure of the individual. However, relatively few persons who have failed to develop silicosis after prolonged exposure have been examined post mortem, since clinical interest centers on those with "positive" findings. Further study of the negative cases is essential because the "positives" are so frequently complicated by widespread pulmonary infection, which minimizes the value of the post-mortem studies. Reaction to infection obscures slight anatomic evidences of pneumoconiosis, and large amounts of inflammatory exudate or scar tissue increase the quantity of tissue elements in the lungs together with their inorganic constituents. As a consequence, there is a high dilution factor for exogenous minerals that gives a false impression of quantity based upon dry lung tissue. Comparisons, therefore, may be misleading.

A number of lung specimens are now available from persons long employed in silica industries who developed little or no silicosis and who died of causes other than disease of the lungs. All of these subjects had been employed in industries where many cases of obvious silicosis had developed and where, in most instances, silicotic lungs have been subjected to similar methods of investigation. The subjects were chiefly hematite and magnetite miners and their employment periods varied from seven to twenty years. These lungs are being re-analyzed to determine separately the amount of total silica and of free silica both in the lungs and in the lymph nodes that drain these organs. For the silica determinations both chemical and X-ray diffraction techniques are being employed. Histologic examination of these lungs generally reveals silicotic nodular fibrosis in the lymph nodes but not in the lungs unless there are scars of healed tuberculosis to cause local accumulations of silica dust. Chemical analyses of the lungs thus far completed usually show silica values that are higher than those for nonexposed subjects but are considerably lower than those for persons with silicosis. For the draining lymph nodes, the silica values may approximate those for cases of frank silicosis, although there are frequent exceptions. The work on differentiation between free silica and combined silica has not progressed far enough for comment. The study thus far might indicate either that less dust had entered the lungs which show minimal changes, or that, having entered, the dust might have been more rapidly and more completely eliminated by a particularly effective lymphatic system.

Subtile mechanisms: More recently it has been proposed that the observed variations in the response of different individuals to similar atmospheric dust concentrations are due to the action of more subtile mechanisms inherent in the

tissues or to the metabolism of the host. It has been pointed out that not all persons are equally susceptible to bacterial infections and toxins, and to various poisons and that, since silica is not a mechanical but a chemical irritant, it might readily be more injurious to some subjects than to others.

These hypothetical explanations for heightened susceptibility in the host are being investigated from several angles in a more or less systematic manner. The published data on the findings in large groups of human beings exposed have been re-examined. They unquestionably substantiate the premise that not all exposed persons develop silicosis although the proportion of affected individuals becomes larger with increasing duration of exposure. Moreover, the higher the total concentration of dust and the greater its free-silica content, the greater will be the proportionate involvement of the group. Such data are so seldom assembled in the same form that detailed comparisons between different groups are rarely possible. Even with the assistance of a detailed occupational history and a careful analysis of atmospheric conditions, it is not practicable to define precisely all of the situations in which each individual has been exposed during a lifetime of employment.

VARIATIONS IN ANIMALS

In animal inhalation experiments it has been possible to maintain a fairly uniform concentration and composition of atmospheric dust throughout all parts of small rooms accommodating at least 125 guinea pigs. In a number of such experiments most of the animals have been allowed to live out their normal life span in order to produce maximal stages of tissue reaction. Even with excessive concentrations of pure quartz, of the order of 800 million particles per cubic foot of air, it is usual to discover that certain animals of the group react sooner than others, including even those from the same cage. It has also been observed that the last dozen or more survivors, which are usually sacrificed after two or three years to terminate the experiment, show decidedly less silicosis than others killed or dying at earlier periods. Chemical analysis of their lungs also reveals less silica than is present in those with more fibrosis. With lower dust concentrations (125 million particles per cubic foot of air) the variations cited above are still more marked. In dealing with mixed dusts like those of calcined gypsum and quartz, where flocculation phenomena greatly reduce the concentration of inhalable silica particles, the degree of variation is extreme and not more than 25 per cent of the animals surviving after the first manifestation of specific silicotic changes develop such reaction.

Genetic differences: There is experimental evidence to indicate that not all animals will react with the same intensity to injected silica particles when all natural protective mechanisms, such as those of the respiratory tract, are excluded. For example, the introduction of large numbers of fine quartz particles directly into the blood stream of rabbits or guinea pigs promptly kills the animals. However, very large amounts of the same suspension may be injected into a dog's veins without apparent effect. Why this difference exists we do not know, although we suspect that the real reason is connected somehow with the genetic

basis for the distinction between the species. Such explanation is complicated by the frequent occurrence of marked difference in tissue response of animals of the same species. Whether or not this difference is also genetic as it relates to silica remains to be proved. It appears urgent to discover first whether the tissues of some subjects are more sensitive to known quantities of silica than are the tissues of others. One experiment has already been concluded to establish the minimal effective dose of silica particles, one to three microns in size, necessary to produce definite silicotic reaction within eight months on injection into the blood stream of guinea pigs. Seven groups of 3 to 5 guinea pigs were given individual doses varying from 5 to 50 mg. of silica per animal. In all groups the response was variable, but a dose of 10 mg. was considered the least amount practicable for the purpose. One hundred pigs were then given this dose of one- to three-micron silica in two injections. More than 80 pigs survived a year, at which time they were killed. Their tissues are being studied for the amount of reaction and analyzed to determine the quantity of silica that they contain. This procedure should establish quite definitely whether the tissues of different animals of the same species vary widely in their capacity to react.

Quantity of dust inhaled: In experimentally controlled environmental conditions, where there can be no question of the history of exposure, there is again variation in capacity of the tissue to respond. We do not know the factors responsible. A large group of animals is now being investigated by analyzing separately both the lungs and the associated lymph nodes. There are variations in the severity of tissue reaction occurring in the lungs of different animals killed on the same day, and there is a corresponding variation in the quantity of silica in this tissue. Both the tissue reaction and the chemical demonstration of silica in the lungs are merely indices of the amount of irritant retained in the pulmonary tissue. We still do not know whether all animals in the group inhaled the same quantity of silica. However, if for any particular exposure period the sum of the silica in the lungs and in the nodes should be fairly constant for all animals of the group, then one could assume that the quantity of dust inhaled by each animal was constant. The amount drained from the lungs and transferred to the nodes would account for the differences in pulmonary response between animals.

Particle size of dust inhaled: In view of what has been said of the probable correlation between severity of tissue reaction and local concentration of silica in the particular tissue involved, it might be inferred that consideration of other possible causes of variation would be unprofitable. We know from experimental studies that quartz may be present in tissue without provoking any important reaction. Particles of silica greater than five microns in size are incapable of producing significant tissue response when injected intratracheally, intravenously, or subcutaneously. The failure to react has always been attributed to the reduced amount of surface presented by a given weight of large particles. In contrast, particles smaller than five microns are biologically active in proportion to their surface area. Even in this range, however, there is a species variation. Rabbits exposed by inhalation to a controlled concentration of atmospheric dust

of amorphous silica particles in submicroscopic range developed in two months' time a diffuse chronic cellular pneumonitis which after twelve months failed to become fibrotic. Under the same experimental conditions white rats developed a fibrogenic type of pulmonary response, but it occurred somewhat later, usually within four to six months. Guinea pigs, however, first showed a significant fibrosis only after twenty-four months of continuous exposure to the silica.

Thus, there was a pronounced species variation in the degree and character of the tissue response to an inhaled substance, such as silica, irrespective of the fact that the particles were of submicroscopic size and presumably easily inhaled into the lung. Here the filtering mechanism of the upper respiratory tract does not appear to be a primary factor in determining the observed variation in the different species of animals. The problem of species difference in reaction to inhaled dust becomes more complex when one considers that with quartz dust of large-size particles, one to three microns, the sequence of pulmonary response is rats first; guinea pigs, second; and rabbits, last; while in the instance of amorphous silica the response is rabbits first; rats, second; and guinea pigs, last. Explanation of these species differences might lead to fuller understanding of the nature of the variation observed in industrial experience with human subjects.

Dietary factors: Several empirical tests have been made to learn whether dietary factors suspected of influencing the formation of scar tissue have any effect upon the response to silica. Animals maintained upon diets deficient in vitamin C are said to be incapable of developing fibrosis. Such is not the case in silicotic animals. When injected with pure silica in large doses, guinea pigs with vitamin C deficiency developed silicosis just as rapidly as control animals on normal diets. Feeding brewers' yeast, which contains most of the vitamins of the so-called "B complex," has prevented the development of certain forms of cirrhosis of the liver in rabbits (14). Over a twelve-month period of observation such feeding has not prevented the development of silicotic reactions in the liver or other organs of rabbits injected intravenously with a moderate dose of quartz particles.

Variable biochemical mechanisms: During recent years studies have strengthened the view that the toxic action of silica on lung tissue depends on its chemical interaction with vital components of tissues, specifically of cells. Apparently this effect is exerted only after cellular ingestion of the particle, and does not follow should it remain in the extracellular fluid. The phagocytes are injured or die, and connective tissues undergo a peculiar hyaline transformation. It seems, therefore, that certain biochemical mechanisms might be involved which in a qualitative and a quantitative sense are so variable in different individuals as to account for relative degrees of susceptibility. The mechanisms may be related to the protein molecules, enzyme and co-enzyme systems, large molecular carbohydrates, and lipoid constituents. A hypothesis regarding the latter was advanced by Fallon (15) some few years ago. The presence of droplets of visible fat in the phagocytic cells of both tuberculosis and silicosis suggested to him that it was these nonspecific fatty or lipoid substances, liberated in large amounts

from the injured cell, that led to the formation of the nodules characteristic of each disease. Injection of fatty substances extracted from silicotic tissue produces nodules in experimental animals, but the inability to remove all particulate silica from the fatty substances makes the validity of the lipoidal reaction questionable. Other hypotheses may be advanced which refer to the physicochemistry of the living cell in contact with quartz. We can accept them only as tentative, pending specific proof.

SUMMARY

From a consideration of the many phases of individual variations in pulmonary response to inhaled dust that have been reviewed, it is evident that we have no simple explanation for this puzzling phenomenon. It has been shown that not all subjects exposed to dust under presumably the same environmental conditions react alike. Some are susceptible and respond early; others are partly or almost completely resistant. This condition occurs both with the experimental animal and with the industrial worker inhaling atmospheres contaminated with dust. Various explanations have been offered to account for these differences, but none is entirely satisfactory. Inefficient nasal filtration, physiologic peculiarities of the lungs, chronic infection of the respiratory tract, effectiveness of the lymphatic drainage system, quantity of dust deposited in the lungs, particle size, metabolic and genetic factors, and physicochemical differences have been suggested as possible determinants influencing the degree of pulmonary reaction of the individual man or animal exposed to a dusty environment. The relative importance of each of these elements in the production of pulmonary dust disease in some workers and not in others remains to be determined.

SUMARIO

Variaciones en la Susceptibilidad Individual a los Polvos Industriales Inhalados en los Pulmones

Del estudio de las muchas fases de variaciones individuales en la reacción pulmonar al polvo inhalado que aquí se repasan, resulta evidente que no contamos con ninguna sencilla explicación de este intricado fenómeno. Está demostrado que no todos los sujetos expuestos al polvo en ambientes presuntament idénticos reaccionan del mismo modo. Algunos son susceptibles y responden pronto, otros son parcial o casi totalmente resistentes. Esto sucede tanto en el animal de experimentación como en el obrero industrial al inhalar atmósferas contaminadas con polvo. Se han ofrecido varias explicaciones de esas diferencias, pero ninguna resulta del todo satisfactoria. Como posibles factores determinantes que afectan el grado de reacción pulmonar del hombre o animal dado expuesto a un ambiente polvoso, se han indicado la ineficaz filtración nasal, las peculiaridades fisiológicas de los pulmones, la infección crónica del aparato respiratorio, la efectividad del sistema de canalización linfática, la cantidad de polvo depositado en los pulmones, el tamano de las partículas, los factores metabólicos y genéticos y las diferencias fisicoquímicas.

Está aun por determinar la relativa importancia de cada uno de esos elementos en la producción por el polvo de neumopatía en algunos obreros y no en otros.

REFERENCES

(1) LEHMANN, G.: The dust filtering efficiency of the human nose and its significance in the causation of silicosis, J. Indust. Hyg. & Toxicol., 1935, *17*, 37.

(2) DRINKER, P.: The size frequency and identification of certain phagocytosed dusts, J. Indust. Hyg. & Toxicol., 1925, *7*, 305.

(3) TOURANGEAU, F. J., AND DRINKER, P.: The dust filtering efficiency of the human nose, J. Indust. Hyg. & Toxicol., 1937, *19*, 53.

(4) ROOKS, R.: The bacterial filtering efficiency of the human nose, Am. J. Hyg., 1939, *30*, 7.

(5) LANDAHL, H. D., AND BLACK, S.: Penetration of air-borne particulates through the human nose, J. Indust. Hyg. & Toxicol., 1947, *29*, 269.

(6) FINDEISEN, W.: Ueber das absetzen kleiner, in der luft suspendierter teilchen in der menschcichen lunge bei der atmung, Arch. f. d. ges. Physiol., 1935, *236*, 367.

(7) SAYERS, R. R., AND JONES, R. R.: Silicosis and similar dust diseases, Pub. Health Rep. 1938, *55*, 1453.

(8) VAN WIJK, A. M., AND PATTERSON, H. S.: The percentage of particles of different sizes removed from dust-laden air by breathing, J. Indust. Hyg. & Toxicol., 1940, *22*, 31.

(9) HATCH, T., AND HEMEON, W. C. L.: Influence of particle size in dust exposure, J. Indust. Hyg. & Toxicol., 1948, *30*, 172.

(10) LANDAHL, H. D., AND HERRMAN, R. G.: On the retention of air-borne particulates in the human nose, J. Indust. Hyg. & Toxicol., 1948, *30*, 181.

(11) LANDAHL, H. D., AND TRACEWELL, T.: Penetration of air-borne particulates through the human nose, J. Indust. Hyg. & Toxicol., 1949, *31*, 55.

(12) DAVIS, C. N.: Inhalation risk and particle size in dust and mist, Brit. J. Indust. Med., 1949, *6*, 245.

(13) WILSON, I. B., AND LAMER, V. K.: The retention of aerosol particles in the human respiratory tract as a function of particle radius, J. Indust. Hyg. & Toxicol., 1948, *30*, 265.

(14) VONGLAHN, W. C., AND FLINN, F. B.: The effect of yeast on the incidence of cirrhosis produced by lead arsenate, Am. J. Path., 1939, *15*, 771.

(15) FALLON, J. T.: Specific tissue reaction to phospholipids: A suggested explanation for the similarity of the lesions of silicosis and pulmonary tuberculosis, Canad. M. A. J., 1937, *36*, 223.

DISSOCIATION OF THE TUBERCLE BACILLUS[1]

A Review

WILLIAM STEENKEN, JR.

INTRODUCTION

In the early days of experimental laboratory research in tuberculosis, the pioneer investigations by Dr. Edward R. Baldwin were a guiding light to many of the men who are now leaders in this field. In his researches, Doctor Baldwin was meticulous in the extreme, and his caution and sound judgment in the interpretation of his results made his carefully reported conclusions unassailable. He insisted that those who did basic work, whether it was in bacteriologic diagnosis or in the development of an immunizing or therapeutic agent against tuberculosis, should have a thorough knowledge of the tubercle bacillus. It therefore seems fitting, as a tribute to Doctor Baldwin, that we review one of the major advances in the biology and bacteriology of the tubercle bacillus, that is, the dissociation phenomenon. Since it is impossible to review all the work on dissociation by the various investigators, the reader is referred to the comprehensive bibliography at the end of this article.

TERMINOLOGY

A critical review of the literature on dissociation of the tubercle bacillus reveals that, up to the present time, the terminology employed in describing dissociants isolated from different strain sources is loose and haphazard. Many investigators have employed the same, or a slightly modified, nomenclature in classifying dissociants of the tubercle bacillus as has been used for other bacteria. A more exact terminology applicable to the tubercle bacillus alone is needed in order to describe with precision the dissociants as to strain source, virulence, and growth morphology.

The dissociation of the avian and bovine strains of tubercle bacilli was first described by Petroff in 1927 (56, 57). At that time Petroff separated both strains into dissociants and designated one *R* (rough), and the other *S* (smooth) to describe the colony growth characteristics without reference to virulence. These same terms, *R* and *S*, were used by Petroff, Branch, and Steenken in 1929 (60) in reporting on the dissociation of BCG, but with a different connotation; *R* denoting avirulence and *S* denoting high virulence for guinea pigs. In further biological studies on BCG published in 1930 (62), Petroff and Steenken used the terms *R* and *S* in a third sense, *R* meaning resistant to environment and the symbol *S* meaning sensitive to environment. From this point on the terminology acquired diverse meanings as other investigators began to study and apply the dissociation phenomenon to the tubercle bacillus, some using the already misleading symbols, others adopting or adding new terms in reporting their findings. Consequently, it was difficult to compare the studies of the various investigators and evaluate their results.

[1] From The Trudeau Laboratory of The Trudeau Foundation for the Clinical and Experimental Study of Pulmonary Disease, Trudeau, New York.

In an effort to eliminate the confusion of terms in describing dissociants, the writer, in a paper published in 1935 (111), returned the terms *R* and *S* to their original meanings of *rough* and *smooth*, and appended the modifying symbols *v* and *a* to indicate virulence and avirulence; thus, R_v and R_a, and S_v and S_a. Since that time all work on dissociation published by The Trudeau Laboratory has carried this nomenclature. The Committee on Standard Cultures of the Medical Research Committee of the National Tuberculosis Association adopted it temporarily for designating cultures of tubercle bacilli being carried in their culture depot at The Trudeau Laboratory. Because this terminology has clarified the issue in our own work, we propose that it be considered for adoption by other investigators. Since certain strains of tubercle bacilli have produced more than two dissociants, and as there is no uniform relation between colony forms and certain degrees of virulence in the avian, bovine, and human bacillary types of tubercle bacilli, further letters could be added thus: R_{ch} and S_{ch} to indicate chromogenicity, and R_{in} and S_{in} to denote intermediate virulence.

VIRULENCE

Tubercle bacilli are virulent, nonvirulent, or of intermediate virulence. Virulence is not necessarily associated with any particular colony form such as has been observed with pneumococcus, where the *smooth* or *S* type is, as a rule, virulent, and the *rough* or *R* type is avirulent. It should be mentioned, however, that, although the virulent forms of pneumococcus belong to the S colonial types, not all S forms are necessarily virulent. The S character, i.e., production of capsular polysaccharides, is a requisite but not a sufficient condition of virulence; undoubtedly some other factor is involved in the cause of virulence. It has been definitely proved that virulent tubercle bacilli give off nonvirulent variants; this same phenomenon has been observed with other bacteria. The loss of virulence for laboratory animals, which usually occurs outside the animal body, has been demonstrated in the cultures R_1 (Saranac Laboratory) and BCG (Calmette-Guérin), which today are known as attenuated human and bovine strains. Originally, they were highly pathogenic for the guinea pig but, after many generations (years) of subculture on artificial media, they lost their ability to produce progressive disease in certain laboratory animals. This type of attenuation is classified as spontaneous, that is, it is not planned but occurs as the result of years of subculture on artificial media. Today we are able to obtain avirulent cultures within a relatively short period of time by controlling one or more factors during subculture on certain types of culture media. Some strains of virulent tubercle bacilli, when grown on a medium of pH 6.2 and permitted to age from three to four months, undergo autolysis of the colonies. Upon these autolysed areas there appears a secondary resistant growth (111, 115). When this secondary growth is picked and subcultured, the resultant colonies present a strikingly different growth appearance from that of the parent R_v colonies. They are nonvirulent for guinea pigs and are termed an R_a growth. Undoubtedly, some such hidden mechanism was involved in the attenuation of the R_1 and BCG cultures, for their loss of virulence for guinea pigs was gradual and over a period of

years. Their marked attenuation was not observable until the R_a microorganisms were present in such large numbers as to obscure the effect of the disease-producing qualities of the few remaining R_v organisms.

REVERSION

Reports of the reverse process, that is, nonvirulent dissociants reverting to virulent forms, are far less common, and have not definitely proved that reversion to the virulent type takes place with the tubercle bacillus as it has been shown to occur with pneumococcus, both *in vivo* and *in vitro*, under certain controlled conditions. There have been a few isolated cases in which the increase of virulence of attenuated tubercle bacilli was reported by: (*1*) animal passage, (*2*) growth on antisera, (*3*) deep-seated growth in synthetic media. These experiments, however, did not prove conclusively that reversion had taken place, since none of the cultures was started by single cell isolation from a typical R_a or S_a colony growth which had retained its typical structure and virulence after many subcultures. Consequently, there may have been a few R_v and S_v microorganisms still present, and these propagated when inoculated into the animal body or when cultured on artificial media. It is a known fact that the typical R_a or S_a dissociants multiply to a limited extent in the animal body, and are slow to propagate on artificial media. The opposite is true of the R_v and S_v forms.

MICROSCOPIC COLONY MORPHOLOGY

More recently, Middlebrook and others (45) have made an important contribution by showing that when the R_v and R_a microorganisms are grown on a liquid or solid media of relatively stable and reproducible composition, the human and bovine R_v strains have a tendency to form microscopic serpentine cords that vary in length and thickness, and are composed of "microbial cells" that are markedly acid-fast and arranged in parallel along the cords. This cord formation seems to be an important factor in determining the ability of virulent cultures to spread on the surface of solid and of liquid media. In contrast, the avirulent dissociants of virulent mammalian strains of tubercle bacilli grow in a more or less nonoriented pattern. Cords are absent and the organisms are less acid-fast than those of virulent dissociants.

MORPHOLOGY

Morphologically, the tubercle bacillus, when freshly smeared from sputum, tissue, or other body exudates, stained by the Ziehl-Neelsen method, and decolorized with acid alcohol, is a beaded or solidly stained acid-fast rod. When the organism is cultured on artificial media and subsequently smeared and stained, it reveals many nonacid-fast granules and bacilli, as well as many typical acid-fast rods. Upon microscopic examination there appears to be a marked dissimilarity in the structure of the virulent and avirulent dissociants of the microorganisms, but this heterogeneity is more apparent than real and cannot be used as a criterion to differentiate between virulent and avirulent forms, even when the microorganisms are isolated from the same parent strain. It is possible that a

study of the colony structure of organisms isolated by culture from sputum and other body exudates may reveal some factors that would aid in determining the prognosis of the disease in a tuberculous patient, but so far such conclusive data are not available.

One of the most recent and important contributions to the study of the morphology of the tubercle bacillus is the electron microscope. This instrument has shown that at 30,000 magnification the H_{37} R_a and R_v dissociants and other virulent and avirulent tubercle bacilli are surrounded by a uniform membrane, and that this membranous material contains granules. It has been further observed that the organism consists of one or more small nuclear masses within a granular cytoplasm. The nuclear masses vary in size and density and usually contain many granules and small and large vacuoles. However, the electron microscope has failed to reveal any differences between the R_a and the R_v dissociants.

LIFE CYCLE

Studies in the life cycle of the virulent and avirulent dissociants of the tubercle bacillus are open to the same criticism as those that have been done on undissociated strains (34, 35, 40). Wyckoff (124) has recorded growth of an acid-fast organism isolated from a cold-blooded animal by the aid of a motion picture. Aside from this limited report and that of Kahn and others (36), no true evaluation of the life cycle can be made until a more refined method is developed for isolating single cells, both bacillary and coccoid. Acid-fastness and nonacid-fastness must be determined by a vital stain that will not kill the organisms, and the growth observed under a mechanical eye and recorded in motion pictures.

IMMUNIZATION WITH HEAT-KILLED AND LIVING DISSOCIANTS

Heat-killed R_v and R_a and S_v and S_a microorganisms have not produced any greater degree of resistance against subsequent reinfection than undissociated heat-killed microorganisms. Animals vaccinated with living R_a and S_a microorganisms and subsequently reinfected with their parent R_v and S_v strains do not exhibit a higher degree of immunity than animals vaccinated with R_a and S_a microorganisms isolated from unrelated strains. This fact shows that there is no evidence to indicate that the immunity conferred by an avirulent dissociant is type-specific for its homologous virulent dissociant. It has been noted, however, that the avirulent dissociants of different strains vary in their capacity to form protective antibodies in guinea pigs when the animals are reinfected with the same virulent R_v microorganisms (119).

MUTATION

Investigation so far has shown that there is little factual proof that mutation occurs among the human, bovine, and avian strains of tubercle bacilli. It was thought that perhaps the R_a and S_a dissociants of these strains were common ancestors and that by adaptation to a certain environment they would acquire

some specific component and become type-specific of the human, avian, or bovine bacilli. Up to the present time this has not been shown to occur.

CHEMISTRY

Chemical studies on the dissociants of tubercle bacilli have been limited but they have shown that certain differences do exist between the virulent and avirulent microorganisms (118). The application of the newer chemical and physical chemical methods might demonstrate significant differences between the dissociants isolated from the same parent strain. A worth-while study could be made on the H_{37} R_v and R_a dissociants which have been stabilized on Proskauer and Beck's synthetic fluid medium for the past fifteen years. Such steps have already been taken by Dubos and his associates (23, 24, 25). The marked dissimilarity in the physical and the cultural growth characteristics, as well as the slowness of growth of the R_a dissociant as contrasted with the growth of the R_v dissociant on both solid and fluid media, needs further explanation. As previously mentioned, Middlebrook and others have made an important contribution along these lines.

PATHOLOGIC EFFECTS OF DISSOCIANTS OF VARYING DEGREES OF VIRULENCE

Differences in the types of lesions produced by the R_v, S_v, R_a, and S_a microorganisms have been demonstrated. The R_a microorganisms of the human H_{37} strain produce a nonprogressive, proliferative type of disease with little tendency to undergo necrosis; whereas the R_v microorganisms cause a progressive, proliferative type of reaction with marked necrosis. There are many more tubercle bacilli in the lesions of the animals which have been inoculated with the R_v microorganisms, since this dissociant is highly virulent and proliferates rapidly in the animal body. This rapid increase does not occur with the attenuated R_a microorganisms. Rich (78) has described such differences in the types of lesions produced by the dissociants as possibly being the result, not of the direct action of any specific chemical substance possessed by the R_v microorganisms and lacking in the R_a microorganisms, but due merely to the difference in the number of bacilli in the lesions, a factor which is highly important in determining whether a lesion will be small or large, necrotic or nonnecrotic.

More recently, Dubos (21) states that Dr. Hubert Bloch (21a, 21b, 21c), at the New York City Public Health Research Institute, has demonstrated that phagocytic cells in the peritoneal cavity of the mouse ingest both virulent and avirulent forms of tubercle bacilli and that "He further gained evidence that engulfment of the virulent bacilli often resulted in the death and disruption of the phagocyte, a fact not observed with the nonvirulent forms." These observations have since been confirmed by Martin and Pierce (22) of the Rockefeller group, and thereby "provide the first clue to a direct physiological inhibitory effect exerted by the virulent bacilli on normal cells."

DISCUSSION

In this review on dissociation of the tubercle bacillus, one of the main objects has been the attempt to clarify the nomenclature which was employed from the time the phenomenon was observed in 1929 until 1935, when it was suggested to

return the symbols *R* and *S* to their original meanings, and to append the letters *v* and *a* to denote virulence and avirulence. We have also attempted to evaluate certain basic observations relative to the tubercle bacillus that are frequently mentioned in the literature, observations which would seem to require further study before they are accepted as guiding concepts.

In a discussion such as this, it is pertinent also to stress that investigators who are working in the preparation of BCG, or any other attenuated mycobacterium which may be used for vaccination purposes in humans, should have a fundamental knowledge of the viability of the microorganisms in order to ensure vaccines of standard quality. This cannot be overemphasized, especially in view of the fact that BCG vaccines of varying potency have been distributed in this country.

It is hoped that this review of the dissociation of the tubercle bacillus may help to revive interest in further studies in the bacteriology, biology, physiology and the host-organism relationship such as are being carried on by Dubos and his associates at the Rockefeller Institute for Medical Research. A thorough knowledge of these basic principles is imperative in the application of antimicrobial therapy, as well as vaccination methods, in tuberculosis.

REFERENCES

(1) Alexander, E. G.: Dissociation of avian tubercle bacilli, Proc. Soc. Exper. Biol. & Med., 1931, *28*, 686.

(2) Alexander, E. G.: Method for obtaining stable S colonies of human tubercle bacilli, Proc. Soc. Exper. Biol. & Med., 1934, *31*, 1101.

(3) Arloing, F., Thevenot, L., and Viallier, J.: Dissociation directe des colonies R et S en partant des cultures homogènes en bouillon de souches humaines et bovines, Compt. rend. Soc. de biol., 1938, *129*, 584.

(4) Armand-Delille, P. F., and Gavois, H.: Les variétés isolables d'une même-souche de bacille tuberculeux et leur signification, Médecine, 1933, *14*, 382.

(5) Armand-Delille, P.: Étude de la virulence chez le singe (Macacus cynomolgus et cynocéphale) d'une souche S de bacille tuberculeux humain, Compt. rend. Soc. de biol., 1935, *118*, 1194.

(6) Armand-Delille, P., and Bloch, F.: Étude des lésions histologiques pulmonaires provoquées chez le singe par des injections in situ ou intraveineuses à dose élevée d'une souche S de bacille tuberculeux humain, Compt. rend. Soc. de biol., 1935, *119*, 384.

(7) Armand-Delille, P. F.: Caractères biologiques de deux souches de bacille tuberculeux type S, isolées par culture directe du sang, chez de jeunes enfants morts de généralisation tuberculeuse, Compt. rend. Soc. de biol., 1936, *123*, 877.

(8) Barglowski, D.: Recherches sur la dissociation et la morphologie du bacille de Koch, Rev. de la tubere., 1936, *2*, 1076.

(9) Berthelot, A., Valtis, J., and van Deinse, F.: De l'influence de la composition chimique du milieu de culture sur la morphologie des colonies du bacille tuberculeux, Compt. rend. Soc. de biol., 1934, *115*, 1181.

(10) Besta, B.: Untersuchungen über die "Dissoziation" von Tuberkelbacillen, Ztschr. f. Hyg. u. Infektionskr., 1935, *117*, 403.

(11) Birkhaug, K. E.: Étude comparative des colonies dissociées des cultures de bacilles tuberculeux aviaire, bovin et humain, Compt. rend. Soc. de biol., 1933, *113*, 726.

(12) Birkhaug, K. E.: Étude comparative de l'agglutinabilité et des propriétés pathogènes des colonies dissociées en S et R des bacilles tuberculeux aviaire, bovin et humain Compt. rend. Soc. de biol., 1933, *113*, 814.

(13) Birkhaug, K. E.: La courbe du pH des variétés R et S des bacilles tuberculeux dissociés, Compt. rend. Soc. de biol., 1934, *116*, 424.

(14) Birkhaug, K. E.: Études sur la dissociation du *Mycobacterium tuberculosis*. Première partie: Propriétés morphologiques, culturales et physiques des variétés Ch, R et S des colonies de bacilles tuberculeux aviaires et bovins, Ann. Inst. Pasteur, 1935, *54*, 19.

(15) Birkhaug, K. E.: Études sur la dissociation du *Mycobacterium tuberculosis*. Deuxième partie. Propriétés morphologiques culturales et physiques des variétés Ch, R et S de colonies de bacilles tuberculeux humains et de bacilles atténués, Ann. Inst. Pasteur, 1935, *54*, 195.

(16) Birkhaug, K. E.: Monocyte-lymphocyte index and sedimentation reaction as measurements of R and S varieties of *M. tuberculosis* infection, Acta path. et microbiol. Scandinav., Suppl. 26, 1936, p. 130.

(17) Brakier, C. A.: A propos du diagnostic différentiel des divers types de bacilles tuberculeux, Liégé méd., 1937, *30*, 955.

(18) Bühn, S.: Relation between morphology of tubercle bacilli in sputum and clinical aspect of pulmonary tuberculosis, Polska gaz. lek., 1933, *12*, 185.

(19) Denys, P.: Dissociation d'une souche homogène de bacille de Koch en types S et R, Bull. Acad. roy. de méd. de Belgique, 1933, *13*, 69.

(20) Dowd, G. R.: Cultural characteristics of the R1 strain of tubercle bacillus with particular reference to dissociation, Am. Rev. Tubere., 1935, *32*, 50.

(21) Dubos, R. J.: The tubercle bacillus and tuberculosis, Am. Scientist, 1949, *37*, 353.

(21a) Bloch, H.: The relationship between phagocytic cells and human tubercle bacilli, Am. Rev. Tubere., 1948, *58*, 662.

(21b) Allgöwer, M., and Bloch, H.: The effect of tubercle bacilli on the migration of phagocytes *in vitro*, Am. Rev. Tubere., 1949, *59*, 562.

(21c) Bloch, H.: Studies on the virulence of tubercle bacilli isolation and biological properties of a constituent of virulent organisms, J. Exper. Med., 1950, *91*, 197.

(22) Dubos, R. J.: Tuberculosis, Scientific Am., 1949, *181*, 30.

(23) Dubos, R. J., and Middlebrook, G.: Cytochemical reaction of virulent tubercle bacilli (letters to the editors), Am. Rev. Tubere., 1948, *58*, 698.

(24) Dubos, R. J., and Suter, E.: Effect of ammonium ions and aliphatic amines on the ability of virulent mycobacteria to bind neutral red (letters to the editors), Am. Rev. Tubere., 1949, *60*, 384.

(25) Dubos, R. J.: Toxic effects of DL serine on virulent human tubercle bacilli (letters to the editors), Am. Rev. Tubere., 1949, *60*, 385

(26) Eberson, F., and Sweeney, M. A.: Tinctorial transmutations of acid-fast microorganisms and virulence of tubercle bacilli, J. Infect. Dis., 1931, *49*, 303.

(27) Favia, N.: Étude sur la dissociation de quelques souches de bacilles tuberculeux non virulents, Boll. d. sez. ital., d. Soc. internaz. di microbiol., 1934, *6*, 155.

(28) Favia, N.: Sulla dissociazione del bacillo tubercolare (Studio di uno stipite umano avirulento), Ann. d'ig., 1934, *44*, 868.

(29) Frimodt-Möller, J.: Dissociation of tubercle bacilli: Investigations on mammalian types including BCG, Acta tubere. Scandinav., Supp. 2, 1939, p. 3.

(30) Gavrilov, W., and Fester (Mme.): Les divers aspects des colonies du bacille de la tuberculose, Rev. belge de la tubere., 1936, *27*, 385

(31) Guthe, T.: Methylene blue reduction of R and S varieties of *Mycobacterium tuberculosis*, Acta path. et microbiol. Scandinav., Supp. 26, 1936, p. 136.

(32) Jensen, K. A., and Frimodt-Möller, J.: Studies on types of tubercle bacilli isolated from man; dysgonic human tubercle bacilli: Their dissociation and dissociation of one bovine strain, Acta tubere. Scandinav., 1934, *8*, 153.

(33) Jensen, K. A., and Frimodt-Möller, J.: Studies on types of tubercle bacilli isolated from man: Strains with attenuated virulence, Acta tubere. Scandinav., 1936, *10*, 83.

(34) KAHN, M. C., AND SCHWARZKOPF, H.: Single cell dissociation of acid-fast bacteria; mycobacterium of avian tuberculosis; mycobacterium of "rat leprosy," J. Bact., 1933, *25*, 157.

(35) KAHN, M. C.: Further studies on the development cycle of the tubercle bacillus, Nat. Tubere. A. Tr., 1933, *29*, 139.

(36) KAHN, M. C., TAYLOR, E. K., AND SCHWARZKOPF, H.: Moving pictures of the development of bacteria from a single cell, Nat. Tubere. A. Tr., 1935, *31*, 144.

(37) KIRCHNER, O.: Zur Veränderlichkeit des Tuberkuloseerregers in morphologischer Hinsicht, Beitr. z. Klin. Tuberk., 1931, *77*, 72.

(38) KOMIS, A.: Der BCG als abgeschwächter Virus ist dem Humanustypus ähnlich, Beitr. z. Klin. Tuberk., 1931, *78*, 544.

(39) LAPORTE, R.: Dissociation en type R eugonique des souches de bacilles tuberculeux bovin dysgoniques, Compt. rend. Soc. de biol., 1935, *119*, 725.

(40) LAPORTE, R., AND BATTAGLINI, U.: Étude des caractères morphologiques et de la dissociation des bacilles tuberculeux bovins dysgoniques, Compt. rend. Soc. de biol., 1935, *118*, 304.

(41) MACHEBOEUF, M. A., AND DIERYCK, J.: Étude chimiques sur les bacilles tuberculeux: Présence, dans les bacilles de la variante "lisse," d'un haptène de précipitation qui n'existe pas dans la variante "rugueuse," Compt. rend. Soc. de biol., 1935, *119*, 917.

(42) MARCONI, R.: Il bacillo tubercolare nelle forme osteo-articolari studiato dal punto di vista dissociative, Gior. di batteriol. e immunol., 1939, *23*, 782.

(43) MELLON, R. R., RICHARDSON, R. D., AND FISHER, L. W.: Further studies on life cycle of avian tubercle bacillus, Proc. Soc. Exper. Biol. & Med., 1932, *30*, 80.

(44) MIDDLEBROOK, G.: Pathogenic components of the tubercle bacillus: A discussion of recent advances in certain fields of tuberculosis research and postulation of specific component of the tubercle bacillus determining virulence, Am. Rev. Tubere., 1945, *51*, 244.

(45) MIDDLEBROOK, G., DUBOS, R. J., AND PIERCE, C.: Virulence and morphological characteristics of mammalian tubercle bacilli, J. Exper. Med., 1947, *86*, 175.

(46) MUGGIA, A.: Dissociazione o variazione del micobatterio del tubercolo. "Colonie gialle" isolate dal liquor di bambino affetto da meningite tubercolare, Acta paediat., 1938, *22*, 396.

(47) NASTA, M.: Transformation spontanée in vitro d'une souche de bacilles tuberculeux de variété R en variété S, Compt. rend. Soc. de biol., 1937, *125*, 83.

(48) NASTA, M.: Transformation d'une souche de bacilles tuberculeux d'origine humaine (H. Ratti) et d'une souche d'origine bovine (Bov. Cer.) de type R en type S, Compt. rend. Soc. de biol., 1937, *125*, 85.

(49) NASTA, M.: Propriétés pathogènes de bacilles tuberculeux (H. Ratti et Bov. Cer.) de variété S, Compt. rend. Soc. de biol., 1937, *125*, 87.

(50) NASTA, M., AND LUPASCU, I.: Sur un procédé rapide de transformation des bacilles tuberculeux de type "R" en bacilles de type "S," Compt. rend. Soc. de biol., 1938, *129*, 1008.

(51) NASTA, M., AND LUPASCU, I.: Sur la transformation des bacilles tuberculeux humains et bovins de variété "R" en bacilles de variété "S" par passages successifs sur milieu de Loewenstein, Compt. rend. Soc. de biol., 1939, *132*, 587.

(52) NÈGRE, L., AND BRETEY, J.: Sur certaines propriétés biologiques des cultures lisse de bacilles tuberculeux obtenues par la méthode des injections d'extrait acétonique de bacilles de Koch, Compt. rend. Soc. de biol., 1935, *118*, 295.

(53) NUTINI, L. G., THOMAS, G. W., AND SMOLAR, J.: Effect of tissue extracts on growth of avirulent and virulent tubercle bacilli *in vitro*, Stud. Inst. Div. Thom., 1945, *4*, 115.

(54) OATWAY, W. H., JR., AND STEENKEN, W., JR.: Pathogenesis and fate of tubercle produced by dissociated variants of tubercle bacilli, J. Infect. Dis., 1936, *59*, 306.

(55) Oatway, W. H., Jr., and Steenken, W., Jr.: The dissociation of tubercle bacilli, Am. Rev. Tuberc., 1937, *35*, 354.

(56) Petroff, S. A.: Microbic dissociation: The tubercle bacillus, Proc. Soc. Exper. Biol. & Med., 1927, *24*, 632.

(57) Petroff, S. A.: Microbic dissociation: II. The tubercle bacillus, Proc. Soc. Exper. Biol. & Med., 1927, *24*, 956.

(58) Petroff, S. A.: Variability of the tubercle bacillus, New England J. Med., 1929, *200*, 1148.

(59) Petroff, S. A., and Branch, A.: Application of the plate method for isolating single colonies of tubercle bacilli, J. Tech. Methods, 1929, *12*, 135.

(60) Petroff, S. A., Branch, A., and Steenken, W., Jr.: Study of Bacillus Calmette-Guérin (BCG): I. Biological characteristics, cultural "dissociation" and animal experimentation, Am. Rev. Tuberc., 1929, *19*, 9.

(61) Petroff, S. A., and Steenken, W., Jr.: Biological studies of the tubercle bacillus: Microbic dissociation, Nat. Tuberc. A. Tr., 1929, *25*, 155.

(62) Petroff, S. A., and Steenken, W., Jr.: Biological studies of the tubercle bacillus: I. Instability of the organism—microbic dissociation, J. Exper. Med., 1930, *51*, 831.

(63) Petroff, S. A., Steenken, W., Jr., and Schnieder, E. A.: Biologische Untersuchungen über den Tuberkelbacillus; Unstabilität der Organismen; Dissociation der Bakterien, Beitr. z. Klin. Tuberk., 1930, *74*, 499.

(64) Petroff, S. A., and Steenken, W., Jr.: Biological studies of acid-fast organism, Bull. Johns Hopkins Hosp., 1931, *48*, 390.

(65) Petroff, S. A., Steenken, W., Jr., and Winn, W. A.: Immunological studies in tuberculosis: VII. Resistance of chickens sensitized with heat-killed and living avian tubercle bacilli, J. Immunol., 1932, *22*, 413.

(66) Petroff, S. A., and Steenken, W., Jr.: Biological studies of saprophytic acid-fast organisms; Dissociation of *Mycobacterium phlei*, J. Infect. Dis., 1935, *56*, 277.

(67) Petroff, S. A.: The tubercle bacillus: Part I, Quart. Bull. Sea View Hosp., 1937, *3*, 76.

(68) Petroff, S. A.: The tubercle bacillus: Part II, Quart. Bull. Sea View Hosp., 1938, *3*, 185.

(69) Petroff, S. A.: The tubercle bacillus: Part III, Quart. Bull. Sea View Hosp., 1938, *3*, 318.

(70) Petroff, S. A.: The tubercle bacillus: Part IV, Quart. Bull. Sea View Hosp., 1938, *3*, 446.

(71) Pla y Armengol, R.: Die verschiedenen Formen des Tuberkuloseerregers, Beitr. z. Klin. Turberk., 1931, *77*, 47.

(72) Randone, F.: Contributo allo studio della dissociazione del bacillo tubercolare, Gior. di batteriol. e immunol., 1935, *15*, 365.

(73) Reed, G. B., Rice, C. E., and Orr, J. H.: Variation in the antigenic content and colony structure of tubercle bacilli, Nat. Tuberc. A. Tr., 1932, *28*, 147.

(74) Reed, G. B., Orr, J. H., and Rice, C. E.: Studies in variability of tubercle bacilli: BCG, Canad. J. Research, 1934, *11*, 362.

(75) Reed, G. B., and Gardiner, B. G.: Isolation of S and R types by cataphoresis, Canad. J. Research, 1934, *11*, 481.

(76) Rice, C. E., and Reed, G. B.: Studies in variability of tubercle bacilli: Antigenic activity of "S" and "R" cultures as measured by complement-fixation, J. Immunol., 1932, *23*, 385.

(77) Rice, C. E.: Development of precipitins for protein, lipoid and carbohydrate fractions of S and R forms of tubercle bacilli, J. Immunol., 1935, *28*, 19.

(78) Rich, A. R.: The Pathogenesis of Tuberculosis, Springfield, Illinois, Charles C Thomas, 1944.

(79) Rosenberger, R. C.: Dissociation of an old homogenized culture of the human tubercle bacillus, Am. Rev. Tubere., 1937, *35*, 365.

(80) Rosenblatt, M. B., Fullam, E. F., and Gessler, A. E.: Studies of mycobacteria with the electron microscope, Am. Rev. Tuberc., 1942, *46*, 587.

(81) Roulet, F.: Über die Dissoziation des Tuberkelbacillus, Zentralbl. f. d. ges. Tuberk.-Forsch., 1937, *46*, 273.

(82) Sacabejos, H.: Atipismo o mutación del bacilo tuberculoso? A propósito de un estudio, Rev. de hig. y de tuberc., 1932, *25*, 257.

(83) Saenz, A., and Costil, L.: Faits nouveau concernant la dissociation du bacille tuberculeux, Médicine, 1934, *15*, 366.

(84) Saenz, A., and Costil, L.: Propriétés pathogènes, pour la souris, des variantes dissociées R et S du bacille aviaire, Compt. rend. Soc. de biol., 1934, *116*, 836.

(85) Saenz, A., and Costil, L.: Propriétés biologiques des colonies dissocieés R et S de la souche de Calmette et Guérin (BCG), Compt. rend. Soc. de biol., 1934, *116*, 1265.

(86) Saenz, A., Sadettin, M., and Costil, L.: Étude de la toxicité comparée des solutions d'acide sulfurique et d'acide acétique pour les variétés R et S des bacilles tuberculeux des mamifères, Compt. rend. Soc. de biol., 1934, *117*, 308.

(87) Saenz, A., and Costil, L.: Propriétés biologiques et nombre des variétés dissociées en particulier des cultures de bacilles tuberculeux d'origine aviaire, Compt. rend. Soc. de biol., 1934, *117*, 852.

(88) Saenz, A., Sadettin, M., and Costil, L.: Étude de la toxicité comparée des solutions d'acide sulfurique et d'acide acétique pour les variétés R et S des bacilles tuberculeux d'origine aviaire, Compt. rend. Soc. de biol., 1934, *117*, 1072.

(89) Saenz, A., and Costil, L.: Recherches sur la dissociation du bacille de Koch; les différents types bacillaires dérivent-ils d'une souche primitive unique? Presse méd., 1934, *42*, 1827.

(90) Saenz, A., and Costil, L.: Recherches sur les variations biologiques et la dissociation du bacille tuberculeux aviaire, Ann. Inst. Pasteur, 1935, *55*, 518.

(91) Saenz, A.: Degré de virulence des souches aviaires (variété S) récemment isolées et formes anatomo-cliniques de la tuberculose expérimentale provoquée, par vole veineuse, chez la poule et le lapin, Compt. rend. Soc. de biol., 1936, *122*, 362.

(92) Saenz, A.: Dissociation *in vitro* de la variété S en variétés R et Ch des souches de bacilles tuberculeux aviaires récemment isolées, Compt. rend. Soc. de biol., 1936, *122*, 1231.

(93) Saenz, A.: Perte de virulence et stabilité de la variété R d'une souche de bacilles aviaires observées après cinq années de passages *in vitro* sur pomme de terre glycérinée, Compt. rend. Soc. de biol., 1937, *124*, 704.

(94) Saenz, A.: Caractères de culture et classification des colonies dissociées du bacille tuberculeux, en particulier des souches du type aviaire, Compt. rend. Soc. de biol., 1938, *127*, 1054.

(95) Schaefer, W.: La dissociation et la spécificité sériologique des bacilles de la tuberculose aviaire, Compt. rend. Soc. de biol., 1935, *119*, 59.

(96) Schaefer, W.: Sur la classification de certaines souches dite "lisses" de bacilles acido-résistants, Compt. rend. Soc. de biol., 1935, *120*, 590.

(97) Schaefer, W.: Propriétés antigéniques des bacilles tuberculeux bovins lisses et rugueux et des bacilles humains: Présence dans le sérum de lapin antibacilles bovins S d'un anticorps spécifique pour les protéides du bacille bovin, Compt. rend. Soc. de biol., 1939, *130*, 968.

(98) Schnieder, E. A.: Zur Frage der nichtsäurefesten Formen des Tuberkelbazillus, Ztschr. f. Tuberk., 1930, *58*, 247.

(99) Schnieder, E. A.: Sekundärkolonien, Autolyse und Lyse bei der Kultur von Tuberkelbazillen, Ztschr. f. Tuberk., 1930, *59*, 18.

(100) Seibert, F. B., Long, E. R., and Morley, N.: Two avian tubercle bacillus dissociants and two human tubercle bacillus strains of different virulence: Chemical and biologic study, J. Infect. Dis., 1933, *53*, 175.

(101) Severi, R.: Su di ûn raro ceppo di micobatterio della tubercolosi umana isolato in fase S e dissociato spontaneamente in fase Ch, Arch. ital. di med. sper., 1938, *3*, 593.

(102) Sforza, M.: Variazioni patogenetiche presentate da uno stipite di tubercolosi aviare di provenienza bovina, Boll. Soc. ital. di med. e ig. trop., 1946, *6*, 253.

(103) Stamatin, N.: Contributions à l'étude des conditions de la dissociation du bacille de la tuberculose aviaire en deux formes; Smooth et rough, Compt. rend. Soc. de biol., 1938, *127*, 646.

(104) Stamatin, N., and Tomescu, V.: Recherches sur la virulence smooth et rough du bacille tuberculeux aviaire, Compt. rend. Soc. de biol., 1938, *127*, 1348.

(105) Smithburn, K. C.: Colony morphology of tubercle bacilli: Presence of smooth colonies in strains recently isolated from sources other than sputum, J. Exper. Med., 1935, *61*, 395.

(106) Smithburn, K. C.: Colony morphology of tubercle bacilli: Influence of pH of culture medium on colony morphology and virulence, Proc. Soc. Exper. Biol. & Med., 1935, *32*, 1336.

(107) Smithburn, K. C.: Colony morphology of tubercle bacilli: Relation between virulence and colony form, J. Exper. Med., 1935, *62*, 645.

(108) Smithburn, K. C.: Colony morphology of tubercle bacilli: Influence of pH of culture medium on colony form, J. Exper. Med., 1936, *63*, 95.

(109) Smithburn, K. C.: Colony morphology of tubercle bacilli: Influence of pH of culture medium on colony form, virulence and serological behavior, Nat. Tuberc. A. Tr., 1935, *31*, 161.

(110) Steenken, W., Jr., Oatway, W. H., Jr., and Petroff, S. A.: Biological studies of tubercle bacillus: III. Dissociation and pathogenicity of R and S variants of human tubercle bacillus (H37), J. Exper. Med., 1934, *60*, 515.

(111) Steenken, W., Jr.: Influence of pH on dissociation of B Friedländer and *M. tuberculosis*, J. Infect. Dis., 1935, *56*, 273.

(112) Steenken, W., Jr.: Lysis of tubercle bacilli *in vitro*, Proc. Soc. Exper. Biol. & Med., 1935, *33*, 253.

(113) Steenken, W., Jr., and Landau, A.: Dissociation of two unusual acid-fast organisms isolated from human sources, J. Infect. Dis., 1936, *58*, 249.

(114) Steenken, W., Jr., and Smith, M. M.: Culture of tubercle bacilli: I. The effect of sodium hydroxide and sulphuric acid upon acid-fast variants of homologous strains and the influence of the hydrogen ion concentration in different media upon subsequent growth, Am. Rev. Tuberc., 1938, *38*, 503.

(115) Steenken, W., Jr.: Spontaneous lysis of tubercle bacilli on artificial media, Am. Rev. Tuberc., 1938, *38*, 777.

(116) Steenken, W., Jr.: Effect of egg oil on tubercle bacilli: A study on the growth and macroscopical appearance of tubercle bacilli variants of H37, R1 and undissociated strains, Am. Rev. Tuberc., 1940, *42*, 422.

(117) Steenken, W., Jr.: The isolation of purified protein derivatives and carbohydrates from tuberculins and their biological properties, J. Biol. Chem., 1941, *141*, 91.

(118) Steenken, W., Jr., and Gardner, L. U.: Vaccinating properties of avirulent dissociates of five different strains of tubercle bacilli, Yale J. Biol. & Med., 1943, *15*, 393.

(119) Steenken, W., Jr., and Gardner, L. U.: R1 strain of tubercle bacillus: Its dissociation and virulence of variants in normal and silicotic guinea pigs, Am. Rev. Tuberc., 1946, *54*, 51.

(120) Steenken, W., Jr., and Gardner, L. U.: History of H37 strain of tubercle bacillus, Am. Rev. Tuberc., 1946, *54*, 62.

(121) URQUIJO, C. A.: Sobre attenuación de virulencia del bacilo tuberculoso aviario biliado, Rev. argent. de tubere., 1943, *9*, 204.

(122) VAN DEINSE, F.: Dissociation d'une souche de bacilles tuberculeux virulents de type bovin "dysgonique" en une variante avirulente également "dysgonique" et une variante virulente "eugonique" après séjour prolongé dans un liquide pleural de cobaye, Ann. Inst. Pasteur, 1946, *72*, 424.

(123) VAN DEINSE, F.: Variabilité de la virulence d'une souche de bacilles tuberculeux biliés au cours de l'infection chez le cobaye, Ann. Inst. Pasteur, 1946, *72*, 567.

(124) WYCKOFF, R. W. G.: A micro-motion-picture study of the growth of tubercle bacilli from cold-blooded animals, Am. Rev. Tuberc., 1934, *29*, 389.

INHIBITION OF GROWTH OF TUBERCLE BACILLI BY CERTAIN VITAMIN ANALOGUES[1,2]

HILDA POPE AND DAVID T. SMITH

INTRODUCTION

The tubercle bacillus grows readily on a simple synthetic nutrient medium in the absence of vitamins and other accessory growth factors. In a previous report it was shown that under such basic conditions virulent human and bovine strains of the organism synthesize their own supply of the B-complex vitamins (1). Among the vitamins elaborated are *p*-aminobenzoic acid, biotin, folic acid, inositol, nicotinic acid, pantothenic acid, pyridoxine, riboflavin, and thiamine.

This finding stimulated interest in the problem of whether these vitamins are essential in the metabolism of the tubercle bacillus or whether they represent mere waste products of other metabolic processes. If the vitamins could be shown to function in the organism as essential metabolites, it then might be possible to utilize specific vitamin analogues as bacteriostatic agents.

The problem of proving the essential role of the B-complex vitamins in the metabolism of the tubercle bacillus was attacked by utilizing the principle of metabolite antagonism. An attempt was made to block the synthesis or utilization of a given vitamin by the inclusion in the culture medium of analogues related structurally to the metabolite. Such analogues, because of their inability to function as essential metabolites and because of their competitive action with the vitamin at a specific enzyme site, would inhibit growth. The specificity of the inhibitory reaction was determined by testing the ability of a given vitamin to neutralize the bacteriostatic effect when both were included in the culture medium.

Such a survey of the field of the vitamin analogues and their effect on the growth of the tubercle bacillus *in vitro* served a second purpose in that it provided an opportunity for the investigation of a group of compounds which might offer promise as effective chemotherapeutic agents.

EXPERIMENTAL

Two virulent strains of the tubercle bacillus, the human strain, $H_{37}R_v$, and the bovine, Ravenel, were employed as test organisms in this study. Both strains were obtained originally from the Trudeau Laboratory culture collection.

Vorwald's modified Proskauer-Beck medium was used for the growth of both stock and test cultures. Twenty milliliter aliquots of the medium containing the appropriate analogue were dispersed in four-ounce prescription bottles and inoculated with one loopful of organisms from a four-week-old culture. The cultures

[1] From the Department of Bacteriology, Duke University School of Medicine, Durham, North Carolina.

[2] This study was made possible through a grant from the Committee on Medical Research and Therapy of the American Trudeau Society, medical section of the National Tuberculosis Association.

TABLE 1

Analogues of Vitamins, Amino Acids, Purines, and Pyrimidines

NUMBER OF COMPOUND	METABOLITE	ANALOGUE	INHIBITION	REVERSIBILITY
1	*p*-Aminobenzoic acid	Sulfanilamide (3)	+	+
2	*p*-Aminobenzoic acid	Sulfadiazine (4)	+	+
3	*p*-Aminobenzoic acid	Sulfamerazine	+	+
4	*p*-Aminobenzoic acid	Sulfapyridine (3)	+	+
5	*p*-Aminobenzoic acid	Sulfathiazole (3)	+	+
6	*p*-Aminobenzoic acid	4,4′-Diaminodiphenylsulfone (4)	+	+
7	*p*-Aminobenzoic acid	Promin (4)	+	+
8	*p*-Aminobenzoic acid	Diasone (5)	+	+
9	*p*-Aminobenzoic acid	Promizole (5)	+	±
10	*p*-Aminobenzoic acid	4,4′-Diaminodiphenylsulfone-2-sulfonacetamide	+	+
11	*p*-Aminobenzoic acid	4-Propylamino-4′-aminodiphenylsulfone	+	+
12	*p*-Aminobenzoic acid	*p*-Hydroxybenzoic acid	+	−
13	*p*-Aminobenzoic acid	*p*-Methoxybenzoic acid	+	−
14	Biotin	Biotin sulfone (6)	−	−
15	Biotin	γ-(3,4-ureylenecyclohexyl)-butyric acid (7)	−	−
16	Biotin	Desthiobiotin (8,9)	−	−
17	Biotin	4-(imidazolidone-2) caproic acid (10)	+	+
18	Biotin	dl-Homobiotin (11)	+	+
19	Biotin	dl-Norbiotin (11)	+	+
20	Biotin	N-ethyl-N′-(ε-hexanoic acid amide)-carbamide (12)	−	−
21	Biotin	N-ethyl-N′-(ε-ethyl hexanoate) carbamide (12)	−	−
22	Biotin	N-ethyl-N′-(ε-hexanoic acid)-carbamide (12)	−	−
23	Biotin	N-ethyl-N′-n-butane-carbamide (12)	+	−
24	Biotin	N-ethyl-N′-(ζ-ethyl heptanoate)-carbamide (12)	+	−
25	Biotin	N-ethyl-N′-(ζ-heptanoic acid)-carbamide (12)	−	−
26	Biotin	2-hydroxy-4-quinazolinic acid (12)	−	−
27	Biotin	2-hydroxy-3,4-dihydro-4-quinazolinic acid (12)	−	−
28	Biotin	6-isopropyl-pyrimidone-2,4-carboxylic acid (12)	−	−
29	Biotin	4-oxo-5-acetic acid-imidazolidine (12)	−	−
30	Biotin	4-oxo-5-(β-propionic acid)-imidazolidine (12)	−	−
31	Folic acid	2,4-diamino-6,7-dimethylpteridine (13)	−	−
32	Folic acid	2,4-diamino-6,7-diphenylpteridine (13)	−	−

TABLE 1—*Continued*

NUMBER OF COMPOUND	METABOLITE	ANALOGUE	INHIBITION	REVERSIBILITY
33	Folic acid	2-amino-4-hydroxy-6,7-dimethylpteridine (13)	−	−
34	Folic acid	2-amino-4-hydroxy-6,7-diphenylpteridine (13)	−	−
35	Folic acid	Methylfolic acid (14)	−	−
36	Folic acid	Oxyfolic acid	−	−
37	Inositol	γ-hexachlorocyclohexane (15)	+	−
38	Nicotinic acid	Pyridine-3-sulfonic acid (16)		
39	Nicotinic acid	β-acetyl pyridine (17)		
40	Nicotinic acid	β-aminopyridine	−	−
41	Nicotinic acid	2,5-pyridine dicarboxylic acid	−	−
42	Nicotinic acid	Nicotinuric acid	−	−
43	Nicotinic acid	Quinolinic acid	−	−
44	Nicotinic acid	Trigonelline acid sulfate	−	−
45	Nicotinic acid	2-sulfonamido-5-aminopyridine	−	−
46	Nicotinic acid	2-[N-phenyl]-sulfonamido-5-aminopyridine	+	−
47	Nicotinic acid	2-[N-amidino]-sulfonamidopyridine	−	−
48	Nicotinic acid	2-[N-thiazolyl-2]-sulfonamido-5-aminopyridine	+	−
49	Nicotinic acid	2-[N-pyrimidine-2]-sulfonamido-5-aminopyridine	+	−
50	Nicotinic acid	2-[N-(5-bromopyridyl-2)]-sulfonamido-5-aminopyridine	+	−
51	Nicotinic acid	2-[N-(5-chloropyridyl-2)]-5-aminopyridine	+	−
52	Nicotinic acid	2-[N-3,5-dichloropyridyl-2]-sulfonamido-5-aminopyridine	+	−
53	Nicotinic acid	2-[N-3,5-dibromopyridyl-2]-sulfonamido-5-aminopyridine	+	−
54	Nicotinic acid	2-[N-(2-iodopyridyl-5)]-sulfonamido-5-aminopyridine	+	−
55	Nicotinic acid	2-[N-(3,5-diiodopyridyl-2)]-sulfonamido-5-aminopyridine	−	−
56	Nicotinic acid	2-[N-(5-cyanopyridyl-2)]-sulfonamido-5-aminopyridine	+	−
57	Nicotinic acid	2-[N-nicotinamide-6]-sulfonamido-5-aminopyridine	−	−
58	Nicotinic acid	2-[N-nicotinamide-2]-sulfonamido-5-aminopyridine	+	−
59	Nicotinic acid	2-[N-nicotinic acid-6]-sulfonamido-5-aminopyridine	−	−
60	Nicotinic acid	2-[N-(2-iodopyridyl-5)]-sulfonamido-5-aminobenzene	−	−
61	Nicotinic acid	2-[N-(3,5-diiodopyridyl-2)]-sulfonamido-5-aminobenzene	−	−
62	Pantothenic acid	Pantoyltaurine (18)	−	−
63	Pantothenic acid	Pantoyl-n-butylamine (19)	+	−
64	Pantothenic acid	Pantoylisoamylamine (19)	+	−

TABLE 1—*Concluded*

NUMBER OF COMPOUND	METABOLITE	ANALOGUE	INHIBITION	REVERSIBILITY
65	Pantothenic acid	Pantoic amide (20)	−	−
66	Pyridoxine	Desoxypyridoxine (21)	−	−
67	Riboflavin	Galactoflavin (22)	−	−
68	Riboflavin	2,4-diamino-7,8-dimethyl-10-d-ribityl-5,10-dihydrophenazine (23)	+	−
69	Riboflavin	Riboflavin monosuccinate (24)	−	−
70	Riboflavin	Riboflavin trisuccinate (24)	−	−
71	Riboflavin	Riboflavin tetrasuccinate (24)	−	−
72	Riboflavin	Chloral riboflavin (24)	−	−
73	Riboflavin	Diethylaminoacetyl riboflavin citrate (24)	−	−
74	Thiamine	Oxythiamine (25)	−	−
75	Thiamine	2-n-butyl-4-amino-5-pyrimidyl-(2-methyl-3-β-hydroxyethyl)thiazolium bromide (26)	−	−
76	Choline	Tri ethyl choline bromide (27)	−	−
77	Choline	Tri ethyl choline chloride (27)	−	−
78	Vitamin K	2,3-dichloro-1,4-naphthoquinone (28)	+	−
79	Vitamin K	3,3′-methylenebis-(4-hydroxycoumarin) (29)	+	−
80	Alanine	β-alanine (30)	−	−
81	Alanine	Taurine (31)	−	−
82	Alanine	β-aminobutyric acid (31)	−	−
83	Alanine	β-aminoisobutyric acid (31)	−	−
84	Aspartic acid	Cysteic acid (32)	−	−
85	Aspartic acid	Hydroxyaspartic acid (33)	−	−
86	Glutamic acid	dl-methionine sulfoxide (34)	−	−
87	Glycine	Amino methane sulfonic acid (35)	−	−
88	Methionine	Methoxinine (36)	−	−
89	Phenylalanine	β-hydroxyphenylalanine (37)	−	−
90	Phenylalanine	α-amino phenylmethane sulfonic acid (35)	+	−
91	Serine	Isoserine	−	−
92	Tryptophane	Indole-3-acetic acid (38)	+	−
93	Guanine and adenine	Benzimidazole (39)	+	−
94	Guanine	5-amino-7-hydroxy-1-triazole [d] pyrimidine (36)	+	+
95	Uracil	5-methyl-2-thiouracil	−	−
96	Uracil	6-methyl-2-thiouracil	−	−

were incubated at 37° C. in a horizontal position in order to provide optimum conditions for surface growth. The macroscopic appearance and size of the surface pellicle were the sole criteria for determining the effect of the various compounds on growth of the organism.

In a preliminary testing of the compounds, concentrations ranging from 1 to 100 mg. per 100 cc. of medium were used, except in a few cases in which the

supply of the analogue or its low solubility were limiting factors. Four control cultures were included with each experiment, and duplicates run at each concentration level. With the drugs which showed inhibition at these levels, further studies were conducted in order to determine their minimal effective concentration (M. E. C.) and their reversibility by the related vitamin.

The 79 vitamin analogues tested in this study are listed in table 1. Among the analogues of the B-complex vitamins studied were 13 compounds related to *p*-aminobenzoic acid; 17, to biotin; 6, to folic acid; 1, to inositol; 24, to nicotinic acid; 4, to pantothenic acid; 1, to pyridoxine; 7, to riboflavin; and 2 related to thiamine. In addition, two analogues each of choline and vitamin K were tested. Because of the interrelationships between vitamins and the amino acids, and vitamins and the purines and pyrimidines, several analogues related structurally to these compounds also were tested.

Since the majority of the analogues studied are heat stable, they were added directly to the basal medium before autoclaving and the reaction of the medium readjusted to a final pH of 7.0. The riboflavin analogues 69 to 73 were sterilized by filtration through a fritted glass filter. In most cases the culture medium itself was used as the diluent in preparing serial dilutions of the compounds.

Prior to the reversal experiments on the inhibitory analogues, a series of tests were run to determine the effect of the various vitamins, both individually and collectively, on the growth of the tubercle bacillus, and to determine the maximum amounts which could be used without themselves exhibiting a toxic action.

For those analogues initiating any degree of inhibition in the growth of either strain of the tubercle bacillus at concentrations of 100 mg. or less per 100 cc. of medium, the specificity of the reaction was determined by adding the corresponding vitamin to the culture medium containing the analogue, and testing for the ability of the vitamin to neutralize the inhibitory action. The minimum molar concentration of the metabolite effective in neutralizing completely the inhibitory action of the analogue was determined. As used here the *antibacterial index* is expressed as C_I/C_M in which C_I represents the minimum effective molar concentration of the analogue required to inhibit completely the growth of the organism, while C_M signifies the quantity of the related vitamin sufficient to overcome this inhibition of growth.

In addition to the metabolite related specifically to the inhibitory antagonist, reversal of the toxic reaction was attempted with other members of the vitamin B-complex, a combination of these vitamins, various amino acids, purines and pyrimidines, peptone, and a 50 per cent serum medium.

The sulfonamides, sulfones, and 4-(imidazolidone-2) caproic acid were investigated further in a series of experiments on the H_{37} strain in which Dubos liquid medium (2) containing asparagine, inorganic salts, and Tween 80 was used. The cultures were grown in 18 mm. matched test tubes containing a total volume of 10 ml. Two-tenths ml. of a seven-day-old culture was used as the inoculum, and cultures were incubated at 37° C. for fifteen days. Each culture tube was shaken daily to resuspend the organisms which tended to settle out, and to break up the small clumps which formed. The extent of growth was determined by turbidity measurements on the Lumetron photocolorimeter.

RESULTS

In table 2 are listed those compounds whose minimum effective concentration does not exceed 100 mg. per 100 cc. and which were neutralized by the related metabolite.

It may be observed from the tables that, whereas 38 of the compounds inhibited growth of the bacilli, the toxic action of only 14 of these compounds could be completely neutralized by the corresponding metabolite. Among the compounds in which a reversal could be demonstrated were 10 analogues of *p*-amino-

TABLE 2

Comparative Activity of Various Antagonists for the Tubercle Bacillus

ANALOGUE	C_I*	C_M*	$\frac{C_I}{C_M}$*
ST	2.0×10^{-4}	1.5×10^{-6}	13.3
SD	8.0×10^{-4}	1.5×10^{-6}	53.3
SM	7.6×10^{-4}	1.5×10^{-6}	50.7
SP	8.0×10^{-4}	1.5×10^{-6}	53.3
SA	2.9×10^{-3}	1.5×10^{-6}	193.3
S-1	2.0×10^{-4}	1.5×10^{-6}	13.3
S-2	2.6×10^{-4}	1.5×10^{-6}	17.3
S-3	1.9×10^{-4}	1.5×10^{-6}	12.7
S-5	6.9×10^{-4}	1.5×10^{-6}	46.0
S-6	6.6×10^{-4}	1.5×10^{-6}	44.0
ICA	2.5×10^{-5}	2.1×10^{-7}	119.1
HB	3.9×10^{-4}	2.1×10^{-6}	138.1
NB	1.1×10^{-3}	4.1×10^{-6}	268.3
AHTP	1.6×10^{-3}	3.3×10^{-4}	4.8

ST = sulfathiazole; SD = sulfadiazine; SM = sulfamerazine; SP = sulfapyridine; SA = sulfanilamide; S-1 = 4,4′-diaminodiphenylsulfone; S-2 = Promin; S-3 = Diasone; S-5 = 4,4′-diaminodiphenylsulfone-2-sulfonacetamide; S-6 = 4-propylamino-4′-aminodiphenylsulfone; ICA = 4-(imidazolidone-2) caproic acid; HB = homobiotin; NB = norbiotin; AHTP = 5-amino-7-hydroxy-1-triazole [d] pyrimidine.

* Antibacterial index is expressed as C_I/C_M in which C_I represents the minimum effective molar concentration of the analogue required to inhibit completely the growth of the organism, while C_M signifies the quantity of the related vitamin sufficient to overcome this inhibition of growth.

benzoic acid, 3 analogues of biotin, and one compound related to the purine guanine.

A comparison of the activity of the sulfonamides and sulfones against the two strains studied reveals a marked decrease in the effectiveness of both sulfonamides and sulfones when the Ravenel strain is employed as the test organism. This difference is shown more clearly in figure 1 in which the relative effectiveness of these compounds for the two strains is presented graphically and the concentration of each required to produce 100 per cent inhibition is given. The sulfones were found to be far superior to the sulfonamide derivatives as bacteriostatic agents for the bovine strain.

The bacteriostatic effect of the 5 sulfonamide derivatives was neutralized when

a concentration of 0.2 mg. per 100 cc. of *p*-aminobenzoic acid (PABA) was included in the culture medium along with the M. E. C. of the sulfonamide.

The inhibitory effect of 5 of the 6 sulfones studied was reversed by PABA in concentrations comparable to those required for the reversal of sulfonamide activity. It was impossible, however, to obtain complete reversal of the inhibition produced by Promizole. With concentrations of PABA up to one mg. per 100

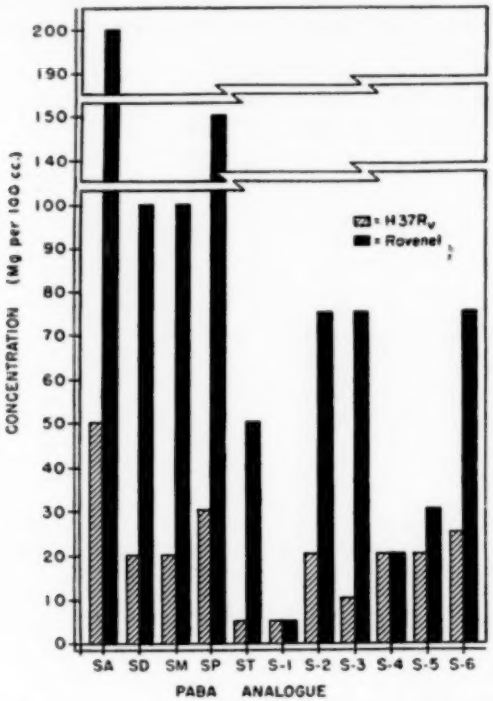


FIG. 1: The effects of various sulfonamides and sulfones on the growth of human and bovine tubercle bacilli. SA = sulfanilamide; SD = sulfadiazine; SM = sulfamerazine; SP = sulfapyridine; ST = sulfathiazole; S-1 = 4,4′-diaminodiphenylsulfone; S-2 = Promin; S-3 = Diasone; S-4 = Promizole; S-5 = 4,4′-diaminodiphenylsulfone-2-sulfonacetamide; S-6 = 4-propylamino-4′-aminodiphenylsulfone.

cc., no reversal was demonstrated. Partial reversal was obtained at 2 mg. per 100 cc. of PABA, at and above which level the vitamin itself is toxic for the organism.

Of the 96 analogues tested against the tubercle bacillus 4-(imidazolidone-2) caproic acid, a compound related to the vitamin, biotin, was the most effective of the drugs for both strains of the organism. A concentration of 0.5 mg. per

100 cc. was sufficient to prevent completely the surface growth of the bacillus, and a level of 0.1 mg. per 100 cc. exerted a demonstrable effect. The activity of this compound was completely neutralized by small amounts of the vitamin. A concentration of 0.005 mg. per 100 cc. (2.1×10^{-7}M) of biotin counteracted the inhibitory effect of 0.5 mg. per 100 cc. (2.5×10^{-5}M) of the analogue.

Norbiotin and homobiotin, a lower and a higher homolog of biotin, also interfered with growth of the organism. In both instances the inhibitory action of the drug could be eliminated by small quantities of biotin. For homobiotin the M. E. C. (10 mg. per 100 cc.) was counteracted by .05 mg. per 100 cc. of the vitamin; the inhibition produced by 25 mg. per 100 cc. of norbiotin was eliminated by 0.1 mg. per 100 cc. of biotin.

Another compound whose antibacterial activity was neutralized by its corresponding metabolite is 5-amino-7-hydroxy-1-triazole [d] pyrimidine. This analogue is structurally related to the purine, guanine. For the H_{37} strain of the bacillus, 25 mg. per 100 cc. of the drug were required to reduce the growth of the organism to a minimum level, while a concentration of 40 mg. per 100 cc. resulted in complete inhibition of growth of the Ravenel strain. Five mg. per 100 cc. of guanine nullified completely the toxic effect of the compound.

When the tests were carried out in Dubos medium, a pronounced bacteriostatic effect was produced at lower concentration levels of the sulfonamides. Sulfathiazole was again the most toxic of the sulfonamides, and the same relative effectiveness of the four other sulfonamides also was observed on this medium. A concentration of 2 mg. per 100 cc. of sulfathiazole reduced the growth of the human-type bacilli to a minimum level as compared to a M. E. C. of 5 mg. per 100 cc. when the organism was cultured on the Proskauer-Beck synthetic medium. The same values were obtained for 4-(imidazolidone-2) caproic acid on both types of media.

DISCUSSION

The findings presented above emphasize the fact that it is insufficient merely to alter the structure of a metabolite in order to produce a compound competitively antagonistic to the vitamin. Of the 79 vitamin analogues studied, only 34 were inhibitory to the bacillus, and of these the action of only 13 could be accredited to an interference with the vitamin metabolism of the organism. In instances of mere inhibition of microbial growth by an analogue of a metabolite, the response is too nonspecific to link the action of the drug with that of the metabolite unless reversal of the effect of the former by the latter can be demonstrated.

Upon the basis of the reversal by the related vitamin of the inhibitory action of the sulfonamides and the sulfones on the tubercle bacillus, it now seems justifiable to state that the *p*-aminobenzoic acid synthesized by the organism in the course of its metabolism serves a functional purpose. The most widely accepted theory, that of Woods and Fildes (40), places PABA in the role of an essential metabolite with which the sulfonamide drugs compete for an important enzyme site on the bacterial cell.

The finding that the inhibitory action of Promizole on the tubercle bacillus could not be neutralized by concentrations of PABA up to a level at which PABA itself becomes toxic raises the question of whether this factor is concerned with the efficacy of the drug as a tuberculostatic agent in experimental animals and in the treatment of tuberculosis in humans. The data obtained indicate that higher concentrations of the vitamin are required to neutralize the minimum effective concentration of Promizole than is necessary for the sulfonamides and other sulfones.

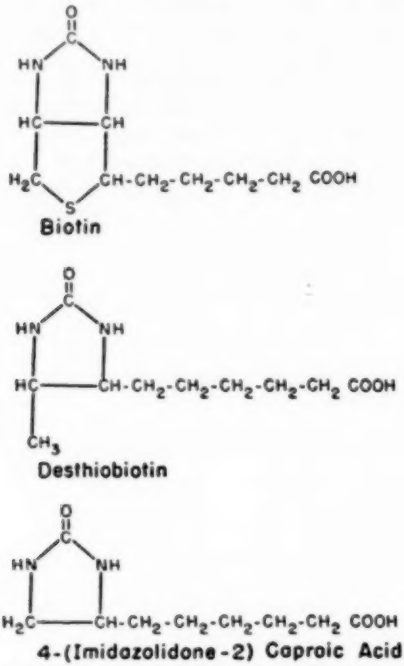


FIG. 2: Structural relationship of the biotin, desthiobiotin, and 4-(imidazolidone-2) caproic acid molecules.

Biotin is an essential metabolite for both human and bovine strains of the tubercle bacillus. Proof for this statement lies in the finding that three analogues related structurally to the vitamin exert a marked *in vitro* bacteriostatic effect on both strains of the organism. The compound, 4-(imidazolidone-2) caproic acid, differs from biotin in that the sulfur ring has been opened and the sulfur removed from the molecule (figure 2). The analogue resembles more closely desthiobiotin, differing from it only in the lack of the terminal methyl group. Homobiotin is a higher homolog of biotin; and norbiotin, its lower homolog, differs from the vitamin only in the length of the carbon chain.

Not only was the growth of the tubercle bacillus completely prevented by three biotin analogues at low concentrations, but small amounts of biotin antagonized this inhibitory action. On the basis of this reversal by the related vitamin, and the ineffectiveness of other compounds as reversing agents, the reaction was considered specific and was accredited to an interference with either the synthesis or utilization of biotin by the bacillus.

The phenomenon of inhibition of growth by a vitamin analogue and its subsequent reversal by the related vitamin was obtained for only two of the B-complex vitamins studied. It cannot be assumed, however, that, because such a phenomenon could not be produced for all of the vitamins, the role of these vitamins for the tubercle bacillus is nonfunctional. This result merely indicates that the particular analogues tested were ineffective as blocking agents in the vitamin metabolism of this microorganism. The observation has been made previously that most vitamin analogues exhibit an inhibitory action only on those bacteria which require the vitamin preformed as a growth factor.

The finding that a derangement in the biotin metabolism of the tubercle bacillus can be produced by analogues of the vitamin which results in a disturbance of the over-all metabolism of the organism is of greater significance than the mere finding of a compound that is effective in stopping the growth of the organisms. Although the translation of the tuberculostatic effects *in vitro* of different compounds into an *in vivo* interpretation requires extreme caution, the efficacy of using such methods as a screening test has been proved. The effectiveness of 4-(imidazolidone-2) caproic acid as a tuberculostatic agent *in vitro* for both human and bovine strains of the bacillus indicates the justification of *in vivo* tests with the compound. Even if this analogue fails to display an effective retardation of progressive tuberculosis, it still might be used as a nucleus about which other potentially tuberculostatic agents might be patterned, with the ultimate goal of designing a compound so altered in structure that it is unable to function in the capacity of biotin in the metabolism of the organism but is still sufficiently similar to the biotin molecule to vie with it competitively at a strategic enzyme site.

SUMMARY

The objectives of this study were: (*1*) to determine whether the vitamins synthesized by the tubercle bacillus serve an essential role in the metabolism of the organism; and (*2*) to survey the field of the vitamin analogues for a possible effective chemotherapeutic agent, the activity of which could be accredited to a derangement of some specific metabolic function.

The problem was attacked by utilizing the theory of vitamin antagonisms in which an attempt was made to block the synthesis or utilization of a given vitamin by the inclusion in the culture medium of analogues related structurally to the vitamin. The specificity of the inhibitory reaction produced was determined by testing the ability of a given vitamin to neutralize the inhibitory effect when both were included in the culture medium.

Seventy-nine vitamin analogues were studied including derivatives of 9 of the

B-complex vitamins, vitamin K, and choline. Thirteen amino acid analogues and 4 analogues of the purines and pyrimidines also were included.

The action of 14 of the analogues could be accredited to a specific inhibition of some essential metabolic reaction. Ten of these were derivatives of *p*-aminobenzoic acid; 3 were related to biotin; and one, to the purine, guanine.

The biotin analogue, 4-(imidazolidone-2) caproic acid, prevented growth of the organism at very low concentrations. The bacteriostatic effect was completely erased by biotin.

It was concluded that: (*1*) *p*-Aminobenzoic acid and biotin are essential factors in the metabolism of the tubercle bacillus. (*2*) On the basis of the *in vitro* results obtained with 4-(imidazolidone-2) caproic acid, *in vivo* studies are indicated. (*3*) 4-(imidazolidone-2) caproic acid is a suitable nucleus about which other potentially bacteriostatic agents might be patterned.

SUMMARIO

Inhibición del Crecimiento de los Bacilos Tuberculosos por Ciertas Vitaminas Análogas

Fueron los objetivos de este estudio: (*1*) determinar si las vitaminas sintetizadas por el bacilo tuberculoso desempeñan un papel esencial en el metabolismo del microbio; y (*2*) examinar el campo de las vitaminas análogas en busca de una posible quimioterapia eficaz cuya actividad pudiera atribuirse a una perturbación de alguna específica función metabólica.

Se abordó el problema utilizando la teoría de los antagonismos vitamínicos, o sea tratando de impedir la síntesis o asimilación de una vitamina dada por la inclusión en el medio de cultivo de elementos análogos relacionados estructuralmente con aquella. Se determinó la especificidad de la reacción inhibidora producida comprobando la capacidad de una vitamina dada para neutralizar el efecto inhibidor al agregar ambos elementos al medio de cultivo.

Los setenta y siete análogos vitamínicos estudiados comprendían derivados de nueve de las vitaminas del complejo B, vitamina K y colina, habiendo además trece análogos de ácidos amínicos y cuatro análogos de las purinas y pirimidinas.

La acción de catorce de los análogos pudo ser imputada a una inhibición específica de alguna esencial reacción metabólica, siendo diez de ellos derivados del ácido *p*-aminobenzoico, y estando tres relacionados con la biotina y uno, guanina, con la purina.

El análogo biotínico, ácido 4-(imidazolidono-2) caproico, impidió el crecimiento del microbio a concentraciones muy bajas. El efecto bacteriostático fué absolutamente erradicado por la biotina.

Dedúcese que: (*1*) el ácido *p*-aminobenzoico y la biotina son factores esenciales en el metabolismo del bacilo tuberculoso. (*2*) A base de los resultados obtenidos *in vitro* con el ácido 4-(imidazolidono-2) caproico, se hallan indicados estudios *in vivo*. (3) El ácido 4-(imidazolidono-2) caproico constituye un núcleo apropiado que puede servir de patrón para otros agentes potencialmente bacteriostáticos.

Acknowledgments

The authors wish to acknowledge the compounds studied in this survey which were generously supplied by the following persons:

Dr. Karl Paul Link, Dept. of Biochemistry, University of Wisconsin, Madison, Wisconsin.
Dr. D. W. Woolley, Rockefeller Institute of Medical Research, New York, N. Y.
Dr. R. J. Major, Merck & Company, Rahway, New Jersey.
Dr. Vincent du Vigneaud, Dept. of Biochemistry, Cornell University Medical School, New York, N. Y.
Dr. Morris Soodak, Dept. of Chemistry, Fordham University, New York, N. Y.
Dr. Albert S. Keston, Biochemical Laboratory, New York University, New York, N. Y.
Dr. Walther K. Ott, Merck & Company, Rahway, New Jersey.
Dr. D. F. Robertson, Merck & Company, Rahway, New Jersey.
Dr. George L. McNew, Naugatuck Chemical Company, Naugatuck, Connecticut.
Dr. Everett M. Schultz, Sharp & Dohme, Inc., Philadelphia, Pennsylvania.
Dr. Karl Folkers, Merck & Company, Rahway, New Jersey.
Dr. M. F. Furter, Hoffmann-La Roche, Inc., Nutley, New Jersey.
Dr. Gustav J. Martin, National Drug Company, Philadelphia, Pennsylvania.
Dr. Louis Laufer, Schwarz Laboratories, New York, N. Y.
Dr. Heinrich Wrelsch, Dept. of Biochemistry, Columbia University, New York, N. Y.
Dr. R. O. Roblin, Jr., American Cyanamid Company, Stamford, Connecticut.
Dr. Francis J. Ryan, Dept. of Zoology, Columbia University, New York 27, N. Y.
Dr. A. C. Bratton, Jr., Parke, Davis and Company, Detroit, Michigan.
Dr. William T. Caldwell and Dr. Edwin J. Fellows, Temple University, Philadelphia, Pennsylvania.
Dr. Robert Duschinsky, Hoffmann-La Roche, Inc., Nutley, New Jersey.
Dr. Philip G. Stansly, American Cyanamid Company, Stamford, Connecticut.
Dr. C. K. Cain, Dept. of Chemistry, Cornell University, Ithaca, New York.
Prof. R. J. Anderson, Sterling Chemistry Laboratory, New Haven 11, Connecticut.
Dr. William Shive, Dept. of Chemistry, University of Texas, Austin, Texas.
Dr. William A. Perlzweig, Dept. of Biochemistry, Duke University, Durham, North Carolina.
Dr. J. A. Aeschlimann, Hoffmann-La Roche, Inc., Nutley 10, New Jersey.

REFERENCES

(1) Pope, H., and Smith, D. T.: Synthesis of B-complex vitamins by tubercle bacilli when grown on synthetic media, Am. Rev. Tuberc., 1946, *54*, 559.

(2) Dubos, R. J., Davis, B. D., Middlebrook, G., and Pierce, C.: The effect of water soluble lipids on the growth and biological properties of tubercle bacilli, Am. Rev. Tuberc., 1946, *54*, 204.

(3) Ballon, H. C., and Guernon, A.: The effect of sulfathiazole and allied compounds on human tubercle bacilli *in vitro*, Am. Rev. Tuberc., 1942, *45*, 212.

(4) Smith, M. I., Emmart, E. W., and Westfall, B. B.: The action of certain sulfonamides, sulfones, and related phosphorus compounds in experimental tuberculosis, J. Pharmacol. & Exper. Therap., 1942, *74*, 163.

(5) Youmans, G. P., Feldman, W. H., and Doub, L.: A comparison of the effect of *p*-amino phenyl sulfone compounds *in vitro* and *in vivo* on tubercle bacilli, Am. Rev. Tuberc., 1946, *54*, 295.

(6) Dittmer, K., du Vigneaud, V., György, P., and Rose, C. S.: A study of biotin sulfone, Arch. Biochem., 1944, *4*, 229.

(7) English, J. P., Clapp, R. C., Cole, Q. P., Halverstadt, I. H., Lampen, J. O., and Roblin, R. O., Jr.: Studies in chemotherapy: IX. Ureylenebenzene and cyclohexane derivatives as biotin antagonists, J. Am. Chem. Soc., 1945, *67*, 295.

(8) DITTMER, K., MELVILLE, D. B., AND DU VIGNEAUD, V.: The possible synthesis of biotin from desthiobiotin by yeast and the anti-biotin effect of desthiobiotin for *L. casei*, Science, 1944, *99*, 203.

(9) LILLY, V. G., AND LEONIAN, L. H.: The anti-biotin effect of desthiobiotin, Science, 1944, *99*, 205.

(10) DITTMER, K., AND DU VIGNEAUD, V.: Antibiotin activity of imidazolidone aliphatic acids, J. Biol. Chem., 1947, *169*, 63.

(11) GOLDBERG, M. W., STERNBACH, L. H., KAISER, S., HEINEMAN, S. D., SCHEINER, J., AND RUBIN, S. H.: Antibiotin effect of some biotin homologs, Arch. Biochem., 1947, *14*, 480.

(12) WRIGHT, L. D., SKEGGS, H. R., AND CRESSON, E. L.: Affinity of avidin for certain analogs of biotin, Proc. Soc. Exper. Biol. & Med., 1947, *64*, 150.

(13) DANIEL, L. J., NORRIS, L. C., SCOTT, M. L., AND HEUSER, G. F.: Growth inhibition of bacteria by synthetic pterins, J. Biol. Chem., 1947, *169*, 689.

(14) MARTIN, G. J., TOLMAN, L., AND MOSS, J.: d(-) Methylfolic acid displacing agent for folic acid, Arch. Biochem., 1947, *12*, 318.

(15) KIRKWOOD, S., AND PHILLIPS, P. H.: The antiinositol effect of γ-hexachloro-cyclohexane, J. Biol. Chem., 1946, *163*, 251.

(16) MCILWAIN, H.: Pyridine-3-sulphonic acid and its amide as inhibitors of bacterial growth, Brit. J. Exper. Path., 1940, *21*, 136.

(17) AUHAGEN, E.: *p*-Aminophenylketone als Antagonisten der *p*-Aminobenzöesoure, Ztschr. f. physiol. Chem., 1942, *274*, 48.

(18) SNELL, E. E.: Growth inhibition by N-(α,γ-dihydroxy-β-β-dimethylbutyryl) taurine and its reversal by pantothenic acid, J. Biol. Chem., 1941, *141*, 121.

(19) SHIVE, W., AND SNELL, E. E.: Growth inhibition by analogues of pantothenic acid: III. N-Pantoylalkylamines and related compounds, J. Biol. Chem., 1940, *160*, 287.

(20) ROSE, F. L., AND SWAIN, G.: Antibacterial substances related to pantothenic acid, Biochem. J., 1945, *39*, 85.

(21) OTT, W. H.: Antipyridoxine activity of 2,4-dimethyl-3-hydroxy-5-hydroxymethyl-pyridine in the chick, Proc. Soc. Exper. Biol. & Med., 1946, *61*, 125.

(22) EMERSON, G. A., WURTZ, E., AND JOHNSON, O. H.: The antiriboflavin effect of galactoflavin, J. Biol. Chem., 1945, *160*, 165.

(23) WOOLLEY, D. W.: Production of riboflavin deficiency with phenazine analogues of riboflavin, J. Biol. Chem., 1944, *154*, 31.

(24) FURTER, M. F., HAAS, G. J., AND RUBIN, S. H.: The preparation and biological activity of some riboflavin derivatives, J. Biol. Chem., 1945, *160*, 293.

(25) SOODAK, M., AND CERECEDO, L. R.: Studies on oxythiamine, J. Am. Chem. Soc., 1944, *66*, 1988.

(26) EMERSON, G. A., AND SOUTHWICK, P. L.: The antithiamine effect of the 2-n-butyl-pyrimidine homologue of thiamine, J. Biol. Chem., 1945, *160*, 169.

(27) KESTON, A. S., AND WORTIS, S. B.: The antagonistic action of choline and its triethyl analogue, Proc. Soc. Exper. Biol. & Med., 1946, *61*, 439.

(28) WOOLLEY, D. W.: Observations on antimicrobial action of 2,3-dichloro-1,4-naphthoquinone, and its reversal by vitamin K, Proc. Soc. Exper. Biol. & Med., 1945, *60*, 225.

(29) GOTH, A.: The antibacterial properties of dicumarol, Science, 1945, *101*, 383.

(30) NIELSEN, N., AND JOHANSEN, G.: Über die Wirkung verschiedener β-alanin-derivate als wuchsstoff oder antiwuchsstoff auf hefe, Naturwissenschaften, 1943, *31*, 235.

(31) NIELSEN, N.: Aufhebung der wuchsstoffwirkung des β-alanins auf hefe durch zusats von taurin, β-aminobuttersäure und anderen substanzen, Naturwissenschaften, 1943, *31*, 146.

(32) RAVEL, J. M., AND SHIVE, W.: Biochemical transformation as determined by competitive analogue metabolite growth inhibitions: IV. Prevention of pantothenic acid synthesis by cysteic acid, J. Biol. Chem., 1946, *166*, 407.

(33) SHIVE, W., AND MACOW, J.: Biochemical transformations as determined by competitive analogue-metabolite growth inhibitions: I. Some transformations involving aspartic acid, J. Biol. Chem., 1946, *162*, 451.

(34) WAELSCH, H., OWADES, P., MILLER, H. K., AND BOREK, E.: Glutamic acid antimetabolites: The sulfoxide derived from methionine, J. Biol. Chem., 1946, *166*, 273.

(35) MCILWAIN, H.: Bacterial inhibition by aminosulphonic analogues of some natural aminocarboxylic acids, Brit. J. Exper. Path., 1941, *22*, 148.

(36) ROBLIN, R. O., JR., LAMPEN, J. O., ENGLISH, J. P., COLE, Q. P., AND VAUGHAN, J. R., JR.: Studies in chemotherapy: VIII. Methionine and purine antagonists and their relation to the sulfonamides, J. Am. Chem. Soc., 1945, *67*, 290.

(37) BEERSTECHER, E., JR., AND SHIVE, W.: Biochemical transformations as determined by competitive analogue-metabolite growth inhibitions: III. A transformation involving phenylalanine, J. Biol. Chem., 1946, *164*, 53.

(38) HANDLER, P., AND KAMIN, H.: Indoleacetic acid and growth of bacteria with varying requirements for nicotinic acid and tryptophane, Proc. Soc. Exper. Biol. & Med., 1947, *66*, 251.

(39) WOOLLEY, D. W.: Some biological effects produced by benzimidazole and their reversal by purines, J. Biol. Chem., 1944, *152*, 225.

(40) WOODS, D. D., AND FILDES, P.: J. Soc. Chem. Ind., 1940, *59*, 133.

THE PATHOGENESIS OF CERTAIN FORMS OF EXTRAPULMONARY TUBERCULOSIS[1,2]

Spontaneous Cold Abscesses of the Chest Wall and Pott's Disease

HUGH E. BURKE

Many writers seem to hold the view that most forms of extrapulmonary tuberculosis are the result of blood-borne dissemination of tubercle bacilli. Critical examination of such data as are available with respect to the routes which tubercle bacilli follow on their way to extrapulmonary sites discloses: (*1*) that some extrapulmonary lesions are undoubtedly a result of lymph-borne dissemination of tubercle bacilli; and (*2*) that convincing evidence with respect to the routes which tubercle bacilli follow on their way to certain extrapulmonary sites is lacking.

The pathogenesis of two forms of extrapulmonary tuberculosis will be considered in the present paper. These two forms of extrapulmonary tuberculosis are: (*1*) spontaneous cold abscesses of the chest wall, and (*2*) Pott's disease.

The observations to be recorded herein will, for convenience, be presented under the following headings:

I. Notes regarding observations of previous investigators
  a) Cold abscesses of the chest wall
  b) Pott's disease
II. Observations concerning pleural lymphatics
  a) Experimental
  b) Anatomical (human)
III. Observations concerning cases of spontaneous cold abscess of the chest wall
IV. Observations concerning cases of Pott's disease
V. Discussion
VI. Summary

I. NOTES REGARDING OBSERVATIONS OF PREVIOUS INVESTIGATORS

Cold Abscesses of the Chest Wall

Examination of the literature dealing with spontaneous cold abscesses of the chest wall reveals that only two investigators, Souligoux (1) and Kaufman (2, 3, 4) apparently have taken a real interest in the mode of origin of these abscesses.

In 1894 Souligoux (1) demonstrated lymph channels in pleuritic adhesions and showed that these channels communicate with lymph vessels in the chest wall. The statements recorded in his paper indicate that he believed that tubercle bacilli are conveyed along these channels to the parasternal lymph nodes. He reported that he had found, in cases of pulmonary tuberculosis and tuberculous empyema which had come to necropsy, that the parasternal lymph nodes are frequently large and caseous. He noted that cold abscesses of the chest wall develop at the sites of the parasternal lymph nodes in a certain

[1] From the Royal Edward Laurentian Hospital, Montreal, Province of Quebec, Canada.

[2] Presented in part before the Medical Section, as part of the symposium on *Laboratory and Research*, at the 45th annual meeting of the National Tuberculosis Association, Detroit, Michigan, May 5, 1949.

number of patients who have had a purulent pleurisy and that these abscesses frequently involve only the soft tissues of the chest wall. He concluded that the breaking down of tuberculous parasternal lymph nodes is a common cause of spontaneous cold abscesses of the chest wall.

Between 1930 and 1933 Kaufman (2, 3, 4) showed, by histologic examination of tissues removed at operation and by dissection of cadavers, that most cold abscesses of the chest wall take origin in caseous parasternal lymph nodes. He, like Souligoux, drew attention to the fact that a goodly number of the cases of cold abscess of the chest wall which he had seen had demonstrable pleurisy.

Pott's Disease

Pott's disease has long been held, as have other forms of skeletal tuberculosis, to be a result of blood-borne dissemination of tubercle bacilli. Convincing evidence for the view that Pott's disease is a blood-borne infection is lacking.

In 1929, Fraser (5), in an unusually interesting and stimulating paper, questioned the then long-held assumption that Pott's disease is a blood-borne infection. He pointed out, as several earlier observers had done, that tuberculosis seems particularly prone to affect the lower thoracic and upper lumbar vertebrae. He expressed a doubt as to whether the extent of cancellous tissue in the vertebrae in this area and the degree of weight-bearing and of movement demanded by this portion of the spine can, as has long been held, adequately explain the predilection of infection, particularly of a blood-borne infection, for this area of the vertebral column. He drew attention to the fact that experimentalists have had peculiar difficulty in reproducing osteomyelitis in any part of the body by injecting tubercle bacilli into the blood stream, and presented some evidence of an experimental, an anatomic, and a clinical nature which suggests that tuberculous prevertebral lymphatic tissue may be a means: (*1*) of direct infection of vertebrae in the thoraco-lumbar region, and (*2*) of changes in the cancellous tissues of vertebral bodies in the same area which predispose these particular vertebrae to the development of tuberculous lesions. Finally, Fraser made it perfectly clear that his statements and observations were not to be construed as a denial of the theory that Pott's disease is a blood-borne infection.

Kaufman (6), whose studies on the mode of origin of cold abscesses of the chest wall have already been referred to, reported in 1936, in a paper on the pathology of Pott's disease, that he believes superficial caries of the spine is a result of the direct spread of infection from overlying caseous nodes. He stated that, when dissecting tuberculous lymphatic chains overlying bone, he had found superficial caries at points at which caseous nodes were in contact with the surface of the bone. He drew attention to the fact that superficial caries of the spine is found at necropsy examination much more frequently than the clinical findings had given himself and others to expect, and he postulated that superficial caries may well be a step in the development of deep caries of the spine.

Key (7) and Amberson (8), in articles which appeared in print in 1940 and which are entitled respectively "The Pathology of Tuberculosis of the Spine" and "Pathogenesis and Medical Treatment of Tuberculosis of the Vertebrae," seem to be content to accept the view that Pott's disease is a sequela of blood-borne dissemination of tubercle bacilli. Key (7), however, makes the statement, after drawing attention to Fraser's (5) contribution, that tubercle bacilli may reach the vertebrae either from the blood stream or from adjacent lymphatic tissue, and may settle there and cause disease.

In 1942, Cleveland and Bosworth (9) reported that, in an effort to learn of the mode of development of spinal tuberculosis, they had examined numerous specimens of human

spine which had been invaded by tubercle bacilli. They stated that their studies revealed that two pathologic processes, singly or in combination, are commonly present in spinal tuberculosis. These they described as: (*1*) caseation of bone and soft tissue; a destructive lesion, due directly to the infection; and (*2*) sclerosis of bone, a vascular phenomenon, due, in all probability, to loss of blood supply from thrombosis or endarteritis, or to occlusion or destruction of blood vessels by the presence of large dissecting abscesses. They made no attempt to trace the sequence of events in the development of spinal tuberculosis. They did, however, make a special point of stating that their observations give them reason to believe that roentgenograms frequently fail to reveal the presence of tuberculosis of the spine and never disclose the full extent of the damage due to the disease.

II. OBSERVATIONS CONCERNING PLEURAL LYMPHATICS

Experimental

In a paper published in 1940, the present writer (10) showed that particulate matter (colloidal thorium dioxide, finely divided lampblack, and tubercle bacilli) introduced into the pleural spaces of guinea pigs is, in part at least, regularly conveyed to two groups of lymph nodes, namely: (*1*) the parasternal lymph nodes, and (*2*) a cluster of retroperitoneal lymph nodes situated close to the descending aorta at the level of the lower thoracic or upper lumbar vertebrae. The latter lymph nodes, which were given the name "para-aortic nodes," will be so designated in the present communication.

It seems best, in view of the fact that the experiments just cited have an important bearing on the present study, to review some of them briefly.

Guinea pigs were injected intrapleurally with a mixture of colloidal thorium dioxide and finely divided lampblack, photographed roentgenologically at intervals, killed at selected periods, and examined macroscopically. To facilitate the injections of the thorium dioxide-lampblack mixture into the pleural space, a three-way petcock, a water manometer, a syringe, and a blunt hypodermic needle were employed. The thorium dioxide preparation used in these experiments was similar to that employed by Menville and Ané (11, 12) in their roentgenographic studies of lymph nodes.

The following protocol contains the findings in a representative guinea pig injected intrapleurally in the manner just described:

In this guinea pig (Number 421), 0.25 cc. of a mixture of colloidal thorium dioxide and finely divided lampblack was introduced into the right pleural space. Chest roentgenograms (postero-anterior and lateral), made a day after the injection, disclosed dense shadows of varied size and shape in both lung fields and several discrete ovoid densities proximate to the shadow of the sternum. Roentgenograms taken five days after the injection and immediately before the guinea pig was killed presented shadows similar to those just described and, in addition, two dense elliptical shadows near the outline of the first lumbar vertebra.

Necropsy examination showed that the visceral and parietal pleurae on both sides were studded with patches of black exudate. The parasternal lymph nodes, which lie external to the parietal pleura in the intercostal spaces close to the lateral borders of the sternum, were jet black. The para-aortic nodes were also jet black. The other lymph nodes, including the tracheobronchial nodes, and the viscera were free from deposits of lampblack.

Stereoscopic examination of roentgenograms of the inflated excised lungs showed dense discrete shadows at the margins of the lung fields. A roentgenogram of the sternum disclosed

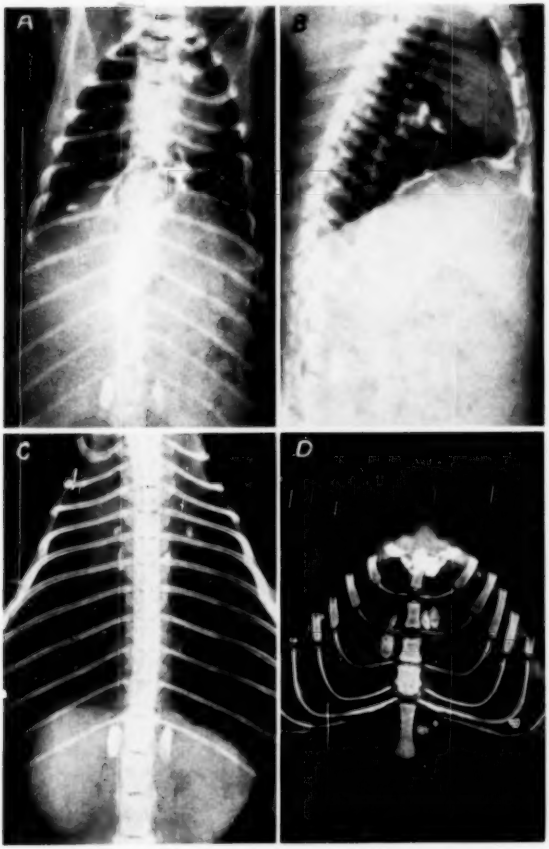


FIG. 1. Guinea pig No. 421

A. Chest roentgenogram (postero-anterior) made on the fifth day. There are dense shadows of varied size and shape in both lung fields and two dense elliptical shadows near the outline of the first lumbar vertebra.

B. Chest roentgenogram (lateral) made on the fifth day. There are ovoid densities proximate to the shadow of the sternum and an elliptical shadow near the outline of the first lumbar vertebra.

C. Roentgenogram of a portion of the vertebral column. Two dense elliptical shadows appear near the outline of the first lumbar vertebra.

D. Roentgenogram of a portion of the chest wall. There are ovoid densities proximate to the shadow of the sternum.

These figures are reproduced through the courtesy of the Journal of Thoracic Surgery, published by the C. V. Mosby Company, St. Louis, Missouri, 1940, **9**, *506-519.*

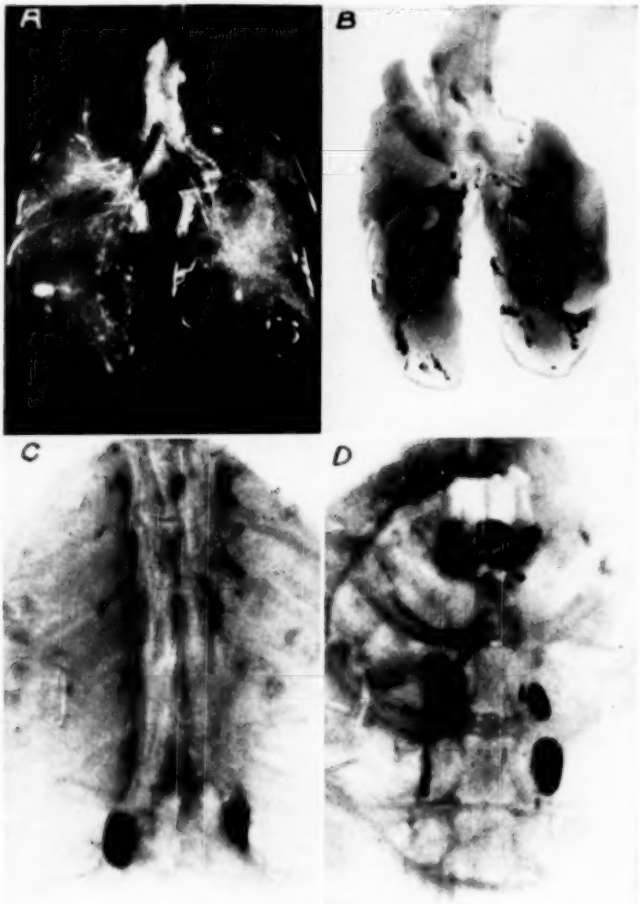


FIG. 2. Guinea pig No. 421

A. Roentgenogram of the excised inflated lungs. Numerous small dense shadows are to be seen. These proved, on stereoscopic examination, to be at the margins of the lung fields.

B. Photograph of the excised lungs. There are black deposits on the visceral pleura of both lungs, but no black material appears in the paratracheal lymph nodes.

C. Photograph of a portion of the vertebral column. There are black deposits on the parietal pleura and large, black para-aortic lymph nodes.

D. Photograph of a portion of the chest wall, showing large black parasternal lymph nodes.

These figures are reproduced through the courtesy of the Journal of Thoracic Surgery, published by the C. V. Mosby Company, St. Louis, Missouri, 1940, **9,** *506-519.*

discrete ovoid densities proximate to the outlines of several of the segments of the sternum. The striking features of a roentgenogram of the torso were two dense elliptical shadows lying close to the shadow of the first lumbar vertebra.

Figures 1 and 2 illustrate the roentgenographic and necropsy findings of this guinea pig.

Vaccinated guinea pigs were injected intrapleurally with a suspension of either avirulent (strain R_1, Saranac Laboratory) or virulent (strain H_{37}, Saranac Laboratory) tubercle bacilli in isotonic saline. The quantity of suspension injected into each animal contained either 0.1 mg. or 1.0 mg. (moist weight) of tubercle bacilli. The guinea pigs were killed at intervals following the intrapleural injection, some on the second day and others at the end of the first, second, third, and fourth weeks, respectively. Necropsy examination of the guinea pigs injected with the larger quantity of tubercle bacilli showed that all had pleuritis in varying degrees and that all had abnormally large parasternal and para-aortic lymph nodes. Necropsy examination of some of the animals injected with the smaller quantity of tubercle bacilli failed to reveal macroscopic evidence of pleuritis, but disclosed enlarged parasternal lymph nodes in all instances and a cluster of unusually large para-aortic lymph nodes in two instances. Examination of sections of the parasternal and para-aortic lymph nodes of many of the guinea pigs revealed characteristic tuberculous lesions in various stages of development. Acid-fast bacilli were found in sections of the parasternal and para-aortic lymph nodes of a number of guinea pigs. Two of the 23 guinea pigs included in this study were found, at necropsy examination, to have enlarged paratracheal and tracheobronchial lymph nodes. The right lung of one of these animals contained an area of pneumonic consolidation of undetermined etiology.

Anatomical Studies

Certain observations on human necropsy material indicating that tubercle bacilli and other particulate matter may be transported (in man, as in the guinea pig) from the pleural spaces to the parasternal and para-aortic lymph nodes were reported in the same paper (10) as that in which the foregoing experimental findings were originally recorded. These observations are briefly as follows:

Necropsy examination of 31 patients, 6 of whom died from extrapulmonary disease and were, as far as could be determined, free from pleuritis; and 25 of whom died from tuberculosis and had pleuritis in various degrees, revealed the following: The parasternal lymph nodes of the 6 cases which presented no signs of pleuritis were small. No lymph nodes were found in the retroperitoneal space, near the vertebral attachments of the diaphragmatic crura, in 5 cases. In contrast to this, one or more of the parasternal lymph nodes of all 25 of the patients with pleuritis were large and abnormal. In addition to this, clusters of lymph nodes were found in the retroperitoneal space near the vertebral attachments of the diaphragmatic crura in 10 of the 25 cases. In one instance, a single isolated caseous abscess (3.0 by 2.0 by 0.5 cm.) was found in the sheath of the psoas portion of the left iliopsoas muscle. This abscess was situated at the level of the above-described retroperitoneal lymph nodes. No macroscopic lesions were found in the vertebrae in the vicinity of this abscess.

The findings in two of the foregoing cases were as follows:

The patients had been iron miners for years before they became ill and died. They had, during the course of their work, inhaled dust containing finely divided magnetite and quartz.

Post-mortem examination showed extensive silico-tuberculosis in both instances. The lungs were jet black. Extensive pleuritic adhesions and a unilateral pocketed pleural effusion were found. There were collections of black material in the pleurae and in many of the pleuritic adhesions. The parasternal lymph nodes were large and dark gray to black. Histologic examination of selected portions of these nodes revealed hyaline silicotic nodules and fibrous tubercles. The lymph nodes situated in the retroperitoneal space, at the level of the vertebral attachments of the diaphragmatic crura, were also large. Some were light gray, others dark gray or black. They, like the parasternal lymph nodes, contained silicotic nodules and tubercles. The thoracic paravertebral nodes were not identified. The mesenteric lymph nodes of both cases were small. They contained no macroscopic black material.

Photographs of the para-aortic lymph nodes of these two cases and of the parasternal nodes in a cadaver have been reproduced in figure 3, A and B, and C, respectively.

The clinical and necropsy findings in a case of miliary tuberculosis with certain unusual complications will be described at this point, as they appear to have a bearing on the present study. This patient came under observation while the foregoing experimental and necropsy studies were in progress. Study of the case revealed: (*1*) clearly defined clinical and necropsy signs of the transport of tubercle bacilli by way of the blood stream to certain ribs with the development of tuberculous abscesses in these ribs; and (*2*) necropsy evidence of the transport of tubercle bacilli by way of lymphatic channels from one or more of the abscesses just described to, in all probability, a paravertebral lymph node with the development of a tuberculous focus in the lateral aspect of a thoracic vertebra adjacent to this node.

The clinical and necropsy findings of this case were as follows:

The patient was admitted to the hospital with moderately advanced pulmonary tuberculosis. His sputum contained tubercle bacilli. He became acutely ill shortly after entering the hospital. Roentgenographic examinations made soon after he became acutely ill revealed signs of miliary tuberculosis and evidence of destructive lesions in the lateral portions of the eighth, tenth, and eleventh ribs on the right side. He died seven weeks after entering the hospital.

Necropsy examination disclosed a large area of tuberculous pneumonia containing a cavity in the upper portion of the left lung, miliary tubercles throughout the remaining portions of both lungs, miliary tubercles in the spleen and in both kidneys, tuberculous abscesses in the lateral portions of the eighth, tenth, and eleventh ribs on the right side and in the fourth rib on the left side, a tuberculous abscess in the lateral portion of the body of the sixth thoracic vertebra, a similar abscess in the lateral portions of the bodies of the fifth lumbar and first sacral vertebrae, and myriads of tubercles in the intercostal channels bordering the fourth to tenth ribs, inclusive, on the right side. Close examination showed that the tubercles in the intercostal lymph channels were limited to the areas between the rib abscesses and the vertebral column, and that only the intercostal lymph channels bordering ribs showing gross evidence of tuberculosis contained tubercles. Comparison of the site of the abscess in the right lateral portion of the sixth thoracic vertebra and the sites at which well-defined collections of pre- and latero-vertebral lymphoid tissue are usually found showed that the level at which the vertebral abscess developed corresponds to the

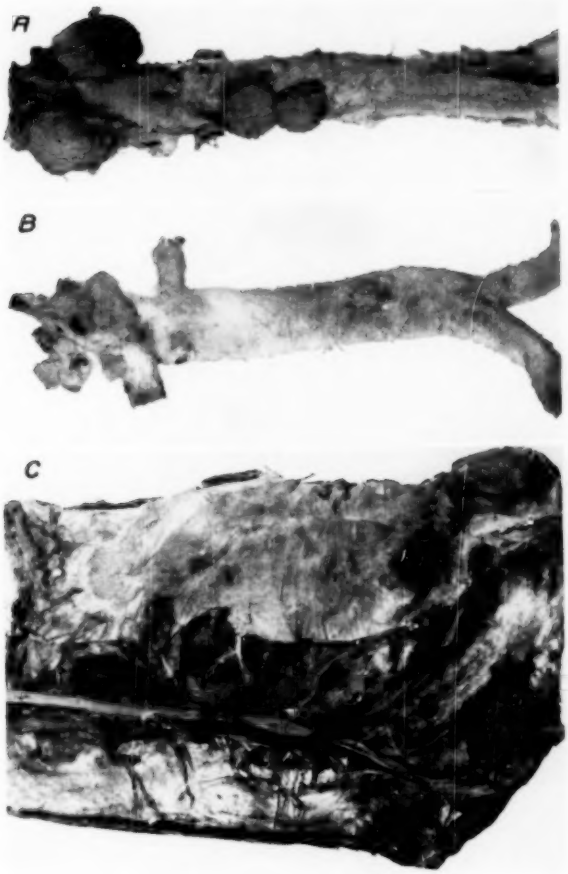


FIG. 3. Human necropsy material

A. Case No. 111. Photograph of abdominal aorta (dorsal surface) and four para-aortic lymph nodes. The cut surface of one of the large nodes is gray to black.

B. Case No. 115. Photograph of abdominal aorta (dorsal surface) and para-aortic lymph nodes. Two small nodes, black on cut surface, and slightly larger pale gray nodes.

C. Photograph of a portion of the sternum of a cadaver. A large parasternal lymph node near the internal mammary vessels at the left-hand side of the photograph. (Courtesy of Dr. Julia Mary Jones)

These figures are reproduced through the courtesy of the Journal of Thoracic Surgery, published by the C. V. Mosby Company, St. Louis, Missouri, 1940, **9**, *506-519.*

level at which the pre- and latero-vertebral lymph nodes commonly become a conspicuous part of the intercostal lymphatic system. The abscess in the lateral portion of the body of

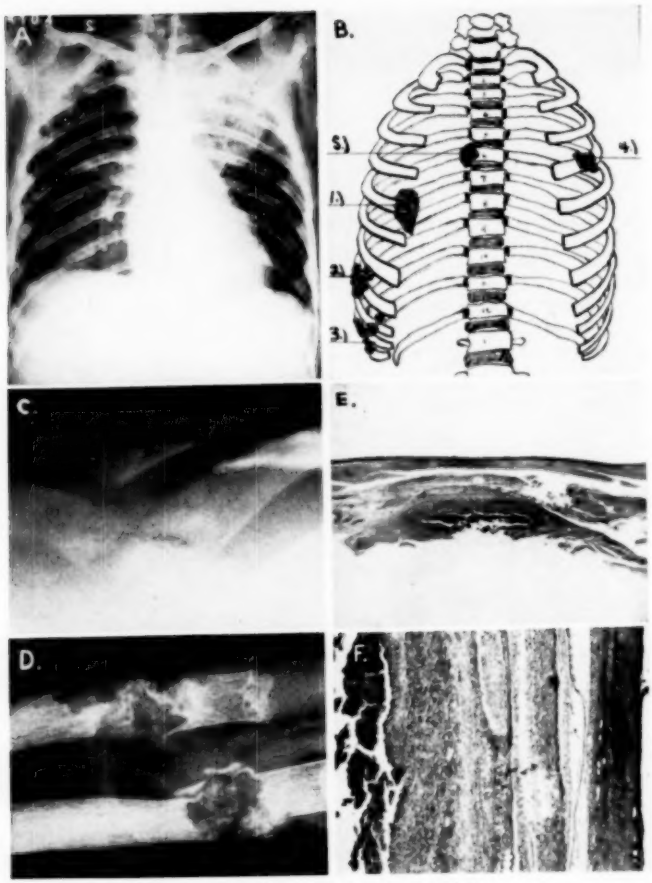


FIG. 4. Human necropsy material

A. Chest roentgenogram taken on January 12, 1937. Abnormal shadows of various densities in the upper one-third of the left lung field. Miliary shadows elsewhere in this lung field and in the right lung field.

B. Sketch of thoracic cage showing sites of tuberculous lesions in the chest wall and in the sixth thoracic vertebra. Abscesses in 1) fifth rib, 2) eighth rib, 3) tenth and eleventh ribs on right side, and 4) fourth rib on left side. 5) Tuberculous lesion in the lateral portion of the body of the sixth vertebra. Dots adjacent to the fourth to tenth ribs, inclusive, on the right side represent small extrapleural lesions.

C. Portion of roentgenogram taken on December 30, 1936. Evidence of breaks in the continuity of the right tenth and eleventh ribs.

D. Roentgenogram of portions of the excised right tenth and eleventh ribs. Signs of extensive destruction of bone.

E. Photomicrograph of portion of parietal pleura and extrapleural lesion from an area near the right tenth rib. Pleura intact. Tuberculous abscess in subpleural tissues. X 25.

F. Photomicrograph of selected area in above-described portion of tissues. Pleura intact. Tuberculous abscess in tissues adjoining pleura. X 75.

*These figures are reproduced through the courtesy of the Transactions of the American Clinical and Climatological Association, 1947, **59**, 122-137.*

the sixth thoracic vertebra contained a sequestrum of bone measuring approximately 0.1 cm. in the longest diameter. A mass of caseous lymph nodes overlay the tuberculous abscesses found in the right lateral portions of the bodies of the fifth lumbar and first sacral vertebrae.

Selected roentgenograms of this case and photographs of some of the findings noted at necropsy examination have been reproduced in figure 4.

III. OBSERVATIONS CONCERNING CASES OF SPONTANEOUS COLD ABSCESS OF THE CHEST WALL

A series of cases (table 1) presenting symptoms and signs indicative of spontaneous cold abscesses of the chest wall was studied in the light of the foregoing observations. Particular attention was paid, in this study, to ascertaining

TABLE 1

Cases of Spontaneous Cold Abscess of the Chest Wall

CASE NUMBER	SEX	AGE	PULMONARY TUBERCULOSIS	ANTECEDENT PLEURISY	COEXISTENT PLEURISY	SITE OF COLD ABSCESS
1	F	50	0	+	+	Parasternal, L. 3
2	M	50	III	+	+	Parasternal, bilateral
3	M	39	II		+	Parasternal, R. 7
4	M	73	III		+	Midclavicular, L. 7
5	F	22	Calcification in hilar region	0	0	Parasternal, R. 4
6	M	41	I		+	Parasternal, R. 4 and 5
7	M	17	I	0	0	Parasternal, L. 7
8	M	30	II	+	+	Parasternal, R. 7
9	M	25	0		+	Parasternal, L. 6
10	M	17	0	+	+	Parasternal, R. 7 Post-axillary, R. 11
11	M	—	I		+?	Parasternal, R. 5
12	F	35	I?	+	0	Parasternal, L. 6, 7, and 8
13	F	39	0	+	+	Parasternal, R. 5 and 6
14	F	5	II	0	0	Parasternal, L. 4

whether or not the patients under review had had a tuberculous pleuritis prior to the development of their chest wall abscesses, or had signs of pleuritis at the time when they came under observation for their chest wall abscesses. In the evaluation of this matter of antecedent or coexistent pleuritis, only those cases in which it was perfectly clear that a tuberculous pleuritis had preceded the development of a chest wall abscess or abscesses were considered cases with an antecedent pleurisy. All of the other patients who presented signs of pleuritis at the time they came under observation for their chest wall abscesses were considered cases with a coexistent pleurisy. Many of the latter presented signs compatible with a pleuritis of long standing. Sufficient data to permit a definite statement with respect to antecedent pleuritis were lacking in a few instances. No attempt was made in these cases to record whether or not there had been an antecedent pleurisy. One patient, in whom a hemidiaphragm appeared on

fluoroscopic examination to be elevated and immobile, but in whom typical roentgenographic evidence of pleuritis was lacking, has been reported as probably having a coexistent pleurisy. Another patient has been recorded, on the basis of a single chest roentgenogram, as probably having minimal pulmonary tuberculosis at the time she came under observation with a chest wall abscess.

Examination of the findings of this series of 14 cases of spontaneous cold abscess of the chest wall (table 1) reveals the following:

The ages of the patients varied from 5 to 73 years. Eight had pulmonary tuberculosis at the time they came under observation for their chest wall abscesses. One patient presented signs suggestive of minimal pulmonary tuberculosis. Another presented signs indicative of calcareous deposits in the tracheobronchial lymph nodes. Six patients had tuberculous pleuritis prior to the development of their chest wall abscesses. Nine of the 14 patients presented clearly defined signs of pleuritis at the time their chest wall abscesses were recognized. One other patient probably had pleuritis at the time he came under observation for a chest wall abscess. The chest wall abscesses, with one or two exceptions, appeared at the margins of the sternum. One abscess appeared in the left midclavicular line; another, in the right posterior-axillary line. Most of the patients had a single abscess. In two cases more than one abscess was present.

These findings, in a slightly larger group of cases of spontaneous cold abscess of the chest wall than that reported in an earlier communication by the present writer (13), seem clearly to support Souligoux's (1) and Kaufman's (2, 3, 4) views concerning the mode of origin of this form of extrapulmonary tuberculosis. The present findings, in conjunction with the findings recorded in the first half of the present paper, indicate that the steps in the evolution of a spontaneous cold abscess of the chest wall are as follows: Tubercle bacilli invade the pleural space and set up a local or widespread pleuritis. Some bacilli are transported from the pleural space to the parasternal lymph nodes. These nodes become caseous and rupture. Necrotic and caseous material burrows externally to form a cold abscess in the chest wall.

IV. OBSERVATIONS CONCERNING CASES OF POTT'S DISEASE

A study of a series of cases (table 2) of Pott's disease, similar to the study of cases of spontaneous cold abscess of the chest wall which has just been described, was carried out. The series now reported consists of a small group of patients, 10 in number, whose findings have already been presented in tabular form (13, 14) and a larger group of patients, 35 in number, who have come under observation and/or treatment in the past five years. The latter group consists of approximately one-half of the total number of patients with Pott's disease admitted to the Royal Victoria Hospital and the Montreal Neurological Institute since 1943. It includes all of the patients, irrespective of age, site of spinal lesion or lesions, et cetera, whose records were sufficiently complete to permit a statement with respect to the presence or absence of signs of pleuritis prior to, or at, the time that a diagnosis of Pott's disease was made. A few of the patients in the present series, whose records were not sufficiently complete to permit a

TABLE 2

Cases of Pott's Disease

CASE NUMBER	SEX	AGE	PULMONARY TUBERCULOSIS	ANTECEDENT PLEURISY	COEXISTENT PLEURISY	SITE OF SPINAL LESION	COMPLICATIONS
1	M	32	II		+	L. 3, 4, and 5	
2	F	45	II	+?	+	T. 11 and 12	
3	F	22	II	+	+	L. 5 and S. 1, 2, and 3	
4	M	33	II	0	0	T. 10 to L. 3	Paravertebral abscess
5	F	31	II	+	+	L. 4 and 5	Psoas abscess
6	F	22	Calcification in hilar region	0	0	L. 5 and S. 1	Psoas abscess
7	M	24	I	+?	0	T. 10 and 11	
8	M	28	II	+	+	T. 10 and 11: L. 4 and 5	Psoas abscess?
9	F	—	Calcification in pulmonary parenchyma	+	+	L. 1 and 2	
10	F	24	II		+	L. 2	
11	F	24	0		0	L. 2	
12	M	50	II	+	0	L. 1 and 2	
13	M	32	III	+	+	L. 3 and 4	
14	M	4	0	+?	+	L. 1 and 2	Paravertebral abscess
15	F	26	I		+	L. 4 and 5	Psoas abscess
16	F	22	II	+	0	T. 12	
17	F	28	I		0	T. 8 and 9	Paravertebral abscess
18	F	22	II	+	+	L. 1 and 2	Calcification near psoas muscle
19	M	21	I		0	T. 4 and 5	Psoas abscess
20	M	20	II	+	+	L. 3, 4, and 5	Paravertebral abscess?
21	M	17	II	+	+	L. 4	Psoas abscess
22	F	4	I	+	0	T. 7 and 8	Paravertebral abscess; tuberculous cervical adenitis
23	F	51	0?	+	+?	T. 4 and 5	
24	F	17	I		0	L. 5	Sinus in sacroiliac region
25	F	31	0		0	L. 2	
26	F	24	0		0	T. 12	Tuberculous cervical adenitis
27	M	20	II	+	+	T. 12: L. 1, 2, and 3	Psoas abscess; tuberculous epidydimitis
28	F	23	I		+	L. 3 and 4	Psoas abscess?
29	F	34	I	+?	0	T. 9, 10, 11	
30	F	27	0		0	L. 5 and S. 1	Tuberculous meningitis
31	M	29	0		0	L. 2	Tuberculous meningitis
32	F	48	0	+	0	T. 5 and 6	Paravertebral abscess; tuberculous meningitis

TABLE 2—*Continued*

CASE NUMBER	SEX	AGE	PULMONARY TUBERCULOSIS	ANTECEDENT PLEURISY	COEXISTENT PLEURISY	SITE OF SPINAL LESION	COMPLICATIONS
33	F	43	Calcification in hilar region		0	T. 11 and 12	
34	F	23	I	+	0	T. 7 and 8	Paravertebral abscess
35	F	26	I?		0	L. 5 and S. 1	
36	M	61	II		+	C. 1, 2, 3, 4, and 5	
37	M	35	I		+	T. 6, 7, 8, 9, and 10	Paravertebral abscess
38	M	31	I	0	0	T. 11 and 12	Paravertebral abscess; myelopathy
39	M	39	I	+	+	T. 10 and 11: L. 1	Paraplegia; Addison's disease
40	M	29	0		+?	Tuberculoma at levels T. 4, 5, 6, and 7	Myelopathy
41	M	25	0	+	+	T. 6 and 7	Paravertebral abscess; paraplegia
42	M	51	Primary complex		0	C. 5, 6, and 7	Myelopathy
43	M	24	0	0	0	L. 3 and 4	Paravertebral abscess; tuberculous meningitis
44	M	24	II	+	+	No demonstrable lesions in vertebrae	Extradural abscess in cervical and thoracic regions; myelopathy
45	M	16	III		+	T. 6, 7, and 8	Paravertebral abscess; paraplegia.

definite statement as to antecedent or coexistent pleurisy but who probably had pleuritis prior to or at the time they came under observation for their Pott's disease, have been handled in a manner similar to the cases of cold abscess of the chest wall where the findings did not permit definite statements.

Examination of the findings of the 45 cases of Pott's disease included in this study (table 2) discloses the following:

The ages of the patients varied from 4 to 61 years. Twenty-nine had pulmonary tuberculosis at the time they came under observation for their Pott's disease. Two presented signs suggestive of pulmonary tuberculosis. One of these has been reported as probably having minimal pulmonary tuberculosis; the other, as probably having no manifest pulmonary disease. Four patients presented signs indicative of calcareous deposits in either the tracheobronchial lymph nodes or the pulmonary parenchyma, or both. Eighteen of the 45 patients definitely had tuberculous pleuritis prior to the time that they were found to have Pott's disease. Four others probably had tuberculous pleuritis before they came under observation. Twenty-one of the 45 patients presented signs of pleuritis at or about the time a diagnosis of Pott's disease was made. Two other patients presented signs suggestive of pleuritis at the time they came under observation. In summary,

27 of the 45 patients, after due allowance for duplication, presented signs of pleuritis before or at the time they were found to have Pott's disease. Most of the spinal lesions involved the lower thoracic and upper lumbar vertebrae. Roentgenograms failed to reveal lesions in the vertebrae or the intervertebral cartilages in 2 cases. In a goodly proportion of the cases paravertebral or psoas abscesses were present. Several of the patients had myelopathic conditions, notably paraplegia. Four had tuberculous meningitis. One had Addison's disease as well as Pott's disease. One patient had tuberculous epidydimitis and two had tuberculous cervical adenitis.

The findings recorded in table 2 and the foregoing statements clearly indicate that tuberculous pleurisy is frequently a precursor, and commonly a concomitant, of Pott's disease. It seems reasonable to point out at this time that the findings recorded herein appear to be in keeping with the view that the transport of tubercle bacilli from the pleural spaces to the para-aortic lymph nodes plays an important role in the pathogenesis of at least some cases of Pott's disease. An attempt will be made in the next section of the present communication to discuss the pathogenesis of Pott's disease in greater detail.

V. DISCUSSION

The experimental findings reviewed herein demonstrate the following: (*1*) that particulate matter, namely, colloidal thorium dioxide, finely divided lampblack, and tubercle bacilli, introduced into the pleural spaces of guinea pigs is, in part at least, regularly transported to the parasternal and para-aortic lymph nodes within a few hours or days of its introduction; and (*2*) that tubercle bacilli introduced into the pleural spaces of vaccinated guinea pigs commonly evoke pleural effusions and frequently give rise to the development of tuberculous lesions in the parasternal and para-aortic lymph nodes.

Menville and Ané (12) appear to be the only investigators who have made an experimental study comparable to the first set of experiments described above. They gave rats, rabbits, and dogs intrapleural injections of colloidal thorium dioxide and attempted, by roentgenographic means, to follow the subsequent course of events. The account of their observations indicates that they probably visualized transport of colloidal thorium dioxide from the pleural spaces to the parasternal lymph nodes in rats, rabbits, and dogs. It suggests that they may, in the case of the rabbit and the dog, have visualized the transport of colloidal thorium dioxide from the pleural spaces to lymph nodes situated in the retroperitoneal space immediately below the diaphragm. The second set of experiments described above appears to be significant in two respects, namely: (*1*) The observations confirm Patterson's (15) work on experimental pleural effusions; and (*2*) they demonstrate that tubercle bacilli introduced into the pleural spaces of vaccinated guinea pigs may not only be transported to the parasternal and the para-aortic lymph nodes but may also evoke the development of tuberculous lesions in these nodes. These experimental findings, more particularly the ones which have to do with the introduction of tubercle bacilli into the pleural spaces of vaccinated guinea pigs, constitute the key to the approach to the study which has culminated in the present communication.

It seems best, at this point, to pause for a moment to make a few special comments concerning the lymph drainage system of the pleural spaces. The experiments just cited demonstrate, it will be recalled, that particulate matter introduced into the pleural spaces of living guinea pigs is, in part at least, promptly transported to two groups of lymph nodes, the parasternal nodes and the para-aortic nodes. The study of human necropsy material reviewed above, presenting, on the one hand, no signs of pleuritis and, on the other hand, signs of pleuritis, seems clearly to indicate that the lymph drainage system of the pleural spaces of man is comparable to that of the guinea pig.

Most observers seemingly agree that the lymph drainage system of the pleural spaces of man communicates with the parasternal lymph nodes or, at least, with some lymph nodes in the anterior mediastinum. Only a few observers, however, appear to have taken note of the fact that the lymph drainage system of the pleural spaces of man and of certain experimental animals regularly communicates with the para-aortic lymph nodes. Cunningham (16) seems to have been the first investigator to point out that some of the lymph channels draining the pleural spaces communicate with lymph nodes below the diaphragm. He noted in a study of the development of the lymphatics of the lungs in the embryo pig that some pleural lymphatics appear to drain into the pre-aortic lymph nodes by way of the ligamentum pulmonale. In 1928 Scott and Beattie (17) noted that in primates and in man there is a cluster of lymph nodes, situated near the descending aorta at the level of the celiac artery, which receives afferents from the lower portion of the thoracic wall. They called these nodes the para-aortic lymph nodes. Scott and Beattie appear to have failed to appreciate the significance of this observation for, in their study of the distribution of tuberculous lesions, they note only that the para-aortic lymph nodes may on occasion become tuberculous when the normal lymph drainage channels of the lungs are blocked. Rouvière (18, 19) in his *Anatomie des Lymphatiques de l'Homme* makes no mention, as far as can be ascertained, of Cunningham's and of Scott and Beattie's observations. He states in his description of the lymphatics of the diaphragm that the subpleural lymph channels of the posterior portion of the diaphragm terminate, among other places, in nodes around the upper portion of the abdominal aorta. He does not, however, make mention of this observation in his description of the abdominal aortic lymph nodes and their afferent and efferent vessels. Failure to appreciate the fact that the lymph drainage system of the pleural spaces of man communicates with the para-aortic lymph nodes as well as with the parasternal lymph nodes has, as will become evident further on in this discussion, seemingly tended to add to the difficulties of tracing the evolution of certain forms of extrapulmonary tuberculosis.

The above-described experimental and anatomic findings, taken in conjunction with the study of 14 cases of spontaneous cold abscess of the chest wall reported herein, seem clearly to indicate that spontaneous cold abscesses of the chest wall are lymph-borne sequelae of tuberculous pleuritis. The findings lend weight, in this respect, to Souligoux's (1) and Kaufman's (2, 3, 4) views concerning the mode of origin of spontaneous cold abscesses of the chest wall. The experimental

findings recorded herein appear to extend the former investigator's observations in that they disclose that tubercle bacilli may be transported from the pleural spaces to the parasternal lymph nodes within a few hours or days of the time when they reach the pleural spaces. This observation suggests that the transfer of tubercle bacilli from the pleural spaces to the parasternal lymph nodes does not, in all probability, have to await the development of lymph channels in pleuritic adhesions.

The conclusion to be drawn from the above-described findings seems to be that the steps in the evolution of most, if not all, spontaneous cold abscesses of the chest wall are as follows:

Tubercle bacilli invade the pleural space and set up a local or widespread pleuritis. Some bacilli are transported from the pleural space to the parasternal lymph nodes. These nodes become caseous and rupture. Necrotic and caseous material burrows anteriorly to form a cold abscess in the chest wall.

The experimental and anatomical findings reviewed, in conjunction with the study of 45 cases of Pott's disease reported above, seem clearly to point to the conclusion that Pott's disease is, in many instances, a lymph-borne sequela of tuberculous pleuritis. The experimental findings demonstrate that tubercle bacilli introduced into the pleural spaces of guinea pigs may, and frequently do, in part at least, escape to the para-aortic lymph nodes and cause tuberculous lesions to develop in these nodes. The observations on human necropsy material suggest that tubercle bacilli which reach the pleural spaces of man may be transported to the para-aortic lymph nodes and may cause tuberculous lesions to develop in these nodes. These observations seem, in the light of the above-described experimental findings, to point to the conclusion that the lymph drainage system of the pleural spaces of man is, insofar as the para-aortic lymph nodes are concerned, comparable to the lymph drainage system of the guinea pig. The necropsy findings in the case of miliary tuberculosis complicated by tuberculous abscesses in several ribs, tubercles in intercostal lymph channels adjacent to some of the abscess-containing ribs, and a tuberculous abscess in the lateral portion of the body of one of the thoracic vertebrae, which is reported above, seem to lend support to Fraser's (5, 20) and Kaufman's (6) observations concerning the spread of tuberculous infection from lymph nodes to underlying bone.

It may not be amiss, since this matter of possible spread of tuberculous infection from lymph nodes to underlying bone is important, to pause at this point to review some of Fraser's (5, 20) and Kaufman's (6) findings in this connection. In 1913 Fraser (20) reported some observations of an experimental nature which appear clearly to indicate that cancellous tissue showing marrow degeneration is peculiarly liable to become infected with tubercle bacilli. He stated in the same communication that he had observed that when a tuberculous lymph node overlies a vertebral body the tissue in the segment adjacent to the node is prone to show degenerative changes which render it liable to infection. In a paper which appeared in 1929, and which has already been referred to in the present communi-

cation, Fraser (5) described two cases showing evidence of transmission of disease processes from lymph nodes to vertebrae.The first of these cases was one in which cancer of a kidney spread by way of lymph channels to a retroperitoneal lymph node and the latter gave rise, presumably by contiguity, to a cancerous process in the eleventh thoracic vertebra. The second was one in which tuberculous disease of the "mesenteric lymph nodes" gave rise to areas of tuberculosis in the anterior portions of the bodies of the eleventh and twelfth thoracic vertebrae. Fraser's words with respect to the manner in which the areas of tuberculosis in the vertebrae developed in the latter case are as follows: "There was evidence that the bone disease was the result of direct lymphatic spread from the infected glandular area." Kaufman's (6) observations concerning the possible spread of tuberculous infection from lymph nodes to underlying bone do not appear to be as detailed as Fraser's (20, 5) observations. He stated in a paper entitled "Anatomie pathologique et pathogenie du mal de Pott," which appeared in print in 1936, that when dissecting tuberculous lymphatic chains overlying bone he had found superficial caries at points at which caseous nodes were in contact with the surface of the bone. In another part of the same paper he drew attention to the fact that superficial caries of the spine is found at necropsy examination more frequently than clinical findings appear to disclose its presence. In still another part he advanced the view that superficial caries may well be a step in the development of deep caries of the spine.

The study of a series of 45 cases of Pott's disease reported above seems to leave no room for doubt that tuberculous pleurisy is frequently a precursor, and commonly a concomitant, of Pott's disease. Examination of the data regarding the site or sites of the spinal lesions in these patients (table 2) reveals that the majority had lesions which involved the lower thoracic and/or the upper lumbar vertebrae. This finding is in keeping with the well-recognized observation that the thoraco-lumbar portion of the vertebral column is the most common site of Pott's disease. Examination of the data in table 2 reveals two points, in addition to the foregoing, which appear to be pertinent to the present discussion. These points are: (*1*) that in a goodly number of the cases paravertebral or psoas abscesses were present; and (*2*) that in only 4 of the 45 cases were clinically evident tuberculous foci present in tissues other than those of the vertebral column, the central nervous system, and the respiratory system. The observation that a goodly number of patients in the present series had paravertebral abscesses seems to be in accord with the view, now generally accepted, that patients with Pott's disease frequently have paravertebral abscesses. The observation that only a few of the patients with Pott's disease had clinically evident extrapulmonary lesions of tuberculous etiology, other than those in the vertebral column and in the central nervous system, appears to be difficult to reconcile with the long-accepted view that all cases of Pott's disease are the result of blood-borne dissemination of tubercle bacilli.

Examination of the salient features of the study described above, in the light of Fraser's (20, 5) and Kaufman's (6) observations and the experimental and anatomical findings reported herein, seems clearly to point to the conclusion that

Pott's disease is, in most instances, a result of lymph-borne rather than blood-borne dissemination of tubercle bacilli. The evidence herein presented indicates that the steps in the evolution of Pott's disease in most cases are somewhat as follows:

Tubercle bacilli invade the pleural space and set up a local or widespread pleuritis. Some bacilli are transported from the pleural space to the para-aortic lymph nodes. Tuberculous lesions develop in these nodes or in other nodes with which they communicate. Some of these lymph node lesions undergo necrosis and caseation. Tuberculous abscesses develop. The tuberculous process in these nodes or abscesses spreads to the vertebral column and its adnexa either by contiguity or by way of communicating lymph channels. One of the end results of this train of events in many instances is, in all probability, Pott's disease.

The view with respect to the mode of origin of Pott's disease which has just been set forth seems to offer a reasonable explanation for the fact that this disease is prone to involve the lower thoracic and the upper lumbar vertebrae, the fact that Pott's disease and paravertebral abscesses are frequently found together, and the fact that patients with Pott's disease seem but rarely to have extrapulmonary lesions of tuberculous etiology other than those in the vertebral column and the central nervous system.

The evidence presented herein does not by any means portray the whole story of the pathogenesis of spontaneous cold abscesses of the chest wall and of Pott's disease. Studies to be carried out in the future, perhaps along lines similar to the present study, will, it is hoped, not only shed further light on the pathogenesis of these two forms of extrapulmonary tuberculosis but will also disclose new avenues of approach to these and certain other extrapulmonary forms of tuberculosis.

SUMMARY

Some of the experimental, anatomical, and clinical findings reported herein demonstrate that spontaneous cold abscesses of the chest wall are, as Souligoux's (1) and Kaufman's (2, 3, and 4) observations indicate, lymph-borne sequelae of tuberculous pleuritis. The steps in the evolution of spontaneous cold abscesses of the chest wall appear to be as follows: Tubercle bacilli invade the the pleural space and set up a local or widespread pleuritis. Some bacilli are transported from the pleural space to the parasternal lymph nodes. These nodes become caseous and rupture. Necrotic and caseous material burrows externally to form a cold abscess in the chest wall.

Some (the remainder) of the experimental, anatomical, and clinical findings recorded herein seem unmistakably to point to the conclusion that most cases of Pott's disease are the result of lymph-borne dissemination of tubercle bacilli. The evidence herein presented indicates that the steps in the evolution of most cases of Pott's disease are, in all probability, somewhat as follows: Tubercle bacilli invade the pleural space and set up a local or widespread pleuritis. Some bacilli are transported from the pleural space to the para-aortic lymph nodes.

Tuberculous lesions develop in these nodes or in other nodes with which they communicate. Some of these lymph node lesions undergo necrosis and caseation. Tuberculous abscesses develop. The tuberculous process in these nodes or abscesses spreads to the vertebral column either by contiguity or by way of communicating lymph channels. One of the end results of this train of events is, in many instances, Pott's disease.

The evidence herein presented does not, it is recognized, portray the whole story of the pathogenesis of tuberculosis of the spine. It does, nevertheless, seem to open up new and significant avenues of approach to this disease and perhaps to certain other forms of extrapulmonary tuberculosis.

SUMARIO

La Patogenia de Ciertas Formas de Tuberculosis Extrapulmonar, a saber: (1) Abscesos Fríos Espontáneos de la Pared Torácica y (2) Mal de Pott

Algunos de los hallazgos experimentales, anatómicos y clínicos aquí presentados demuestran que los abscesos fríos espontáneos de la pared torácica son, según indican las observaciones de Souligoux (1) y Kaufman (2, 3 y 4), secuelas linfóferas de la pleuresía tuberculosa. Los tiempos de la evolución de estos abscesos parecen ser los siguientes: los bacilos tuberculosos invaden el espacio pleural y evocan una pleuresía local o difundida. Algunos bacilos son transportados del espacio pleural a los ganglios linfáticos paraesternales, los cuales se vuelven caseosos y desintegran. Las materias esfaceladas y caseosas horadan al exterior para formar un absceso frío en la pared torácica.

Algunos (los restantes) hallazgos experimentales, anatómicos y clínicos de los aquí expuestos parecen inconfundiblemente señalar la conclusión de que la mayor parte de los casos de mal de Pott son resultado de la diseminación linfófera de bacilos tuberculosos. Los datos presentados indican que los tiempos de la evolución de la mayor parte de los casos de dicho mal vienen, con toda probabilidad, a ser algo por este estilo: los bacilos tuberculosos invaden el espacio pleural y evocan una pleuresía local o difundida. Algunos bacilos son transportados del espacio pleural a los ganglios linfáticos paraaórticos, presentándose lesiones tuberculosas bien en dichos ganglios o en otros comunicados con aquellos. Algunas de esas lesiones ganglionares experimentan necrosis y caseación, formándose abscesos tuberculosos. El proceso tuberculoso de esos ganglios o abscesos se propaga a la columna vertebral ya por contigüidad o por los conductos linfáticos. Uno de los resultados terminales de esa serie de acontecimientos es, en muchos casos, mal de Pott.

Los datos presentados no ofrecen, y así se reconoce, el cuadro completo de la patogenia de la tuberculosis raquídea. No obstante, parece entreabrir nuevas y significativas vías de acercamiento a dicha dolencia y quizás a ciertas otras formas de tuberculosis extrapulmonar.

Acknowledgment

I wish to record my appreciation of the advice and assistance which Dr. Harry A. Bray, of the New York State Hospital, Ray Brook, N. Y., has given me at various times during

the course of the study described herein. I also take pleasure in recording at this time my indebtedness to Dr. W. G. Turner and Dr. J. Gordon Petrie, of the Royal Victoria Hospital, to Dr. Wilder Penfield and Dr. William Cone, of the Montreal Neurological Institute, and to various other friends for placing at my disposal the records of many cases of cold abscess of the chest wall and of Pott's disease which have come under their care in recent years.

REFERENCES

(1) Souligoux: Pathogénie des abcès froids du thorax, Thèse de Paris, 1894.
(2) Kaufman, R.: Pathogénie des abcès froids thoraciques, Paris, 1930.
(3) Kaufman, R.: Quelques considerations sur l'abcès thoracique, J. de chir., 1931, *37*, 829.
(4) Kaufman, R.: De l'abcès froid thoracique, Ann. d'anat. path., 1933, *10*, 541.
(5) Fraser, J.: Tuberculosis of the spinal column, Edinburgh M. J., 1929, *36*, 133.
(6) Kaufman, R.: Anatomie pathologique et pathogénie du mal de Pott, Ann. d'anat. path., 1936, *13*, 81.
(7) Key, J. A.: The pathology of tuberculosis of the spine, J. Bone & Joint Surg., 1940, *22*, 799.
(8) Amberson, J. B.: Pathogenesis and medical treatment of tuberculosis of the vertebrae, J. Bone & Joint Surg., 1940, *22*, 807.
(9) Cleveland, M., and Bosworth, D. M.: The pathology of tuberculosis of the spine, J. Bone & Joint Surg., 1942, *24*, 527.
(10) Burke, H. E.: The role of pleural lymphatics in the pathogenesis of cold abscesses of the chest wall and paravertebral abscesses, J. Thoracic Surg. 1940, *9*, 506.
(11) Menville, L. J., and Ané, J. N.: Roentgen visualization of lymph nodes in animals, J. A. M. A., 1932, *98*, 1796.
(12) Menville, L. J., and Ané, J. N.: A roentgen study of the absorption by the lymphatics of the thorax and diaphragm of thorium dioxide injected intrapleurally into animals, Am. J. Roentgenol., 1934, *31*, 166.
(13) Burke, H. E.: A new concept of the sequelae of tuberculous pleurisy, New Internat. Clin., 1940, *4*, 51.
(14) Burke, H. E.: The pathogenesis of Pott's disease, Tr. Am. Clin. & Climatol. A., 1947, *59*, 122.
(15) Patterson, R. C.: The pleural reaction to inoculation with tubercle bacilli in vaccinated and normal guinea pigs, Am. Rev. Tubere., 1917, *1*, 353.
(16) Cunningham, R. S.: On the development of the lymphatics of the lungs in the embryo pig, Contrib. Embryol., 1916, *12*, 47.
(17) Scott, H. H., and Beattie, J.: Distribution of tuberculous lesions in man and other primates with an account of the lymph glands and vessels of the thorax and upper abdomen, J. Path. & Bact., 1928, *31*, 49.
(18) Rouvière, H.: Anatomie des Lymphatiques de l'Homme, 1932.
(19) Tobias, M. J.: Anatomy of the Human Lymphatic System, by H. Rouvière. 1938.
(20) Fraser, J.: An experimental study of bone and joint tuberculosis, J. Exper. Med., 1913, *17*, 362.

THE PATIENT AND THE PHYSICIAN[1]

JAMES J. WARING

Some weeks ago a spokesman for "organized medicine" made the undiplomatic and altogether wrong statement that the medical profession was primarily interested in its own welfare. General opinion and observation both declare on the contrary that individually the doctor is primarily interested in the welfare of the patient immediately under his hand and eye and that collectively the medical profession is primarily interested in the welfare of the people at large. From ancient times to the present moment the proud tradition of the doctor, sitting in his office or at the bedside of his patient, has been to base his advice invariably upon his conscientious opinion of what was best for that patient. Neither history nor experience has ever shown or will ever show that the physician has lost anything by placing his patient's welfare first.

Although it is only thirty-six years that I have been a doctor, it is forty-five years since I entered medical school and I cannot remember the time when I did not want to be a doctor. It is a source of great family pride that my great-grandfather, grandfather, and one uncle were doctors and that numerous other close and more distant relatives are or have been doctors. It has been my good fortune to serve three separate and extended "hitches" as a "bed-patient," the time so spent numbering in all about nine years. In the very first year of this struggle to regain health, Dr. Lawrason Brown of Saranac Lake told me, and I resented it at the moment, that the day would come when I would be glad I had had tuberculosis. That day has long since come. Serious illness, as it often does, brought compensations beyond my hopes and indeed beyond my deserts. In the words of Shakespeare, "Sweet are the uses of adversity." The pugilist who picks himself up from the mat three times in one battle wins the plaudits of the mob and possibly the bout, but he is apt to leave something of himself on the floor beside his own "claret," perhaps a bit of his wits, and so becomes "punch drunk" the rest of his life! On the other hand, the sick man who fights back to renewed health and strength, who rehabilitates himself, may have lost in his contest a measure of stamina but may have won in its place a precious appreciation of illness not readily secured otherwise. Only today a good woman at the Colorado General Hospital, wrestling with a recurrent malady, said to me quietly: "Doctor Waring, you know serious illness does something for you." What did she mean? She meant to say that one was the beneficiary of serious illness rather than the victim, that serious illness lifted you up spiritually while it beat you down physically. Misfortune often expands both heart and mind into a broader view of our fellow man. It is because of this experience and because the "physician-patient" relationship is much in the press these days that I venture into this field.

Let me first call your attention to the title of this talk, "The Patient and the Physician." Note well the order of these words! I have not said "The Physician

[1] A revision of the "Nu Sigma Nu Address" delivered at the University of Colorado School of Medicine, May 17, 1949, by invitation of the local chapter.

and the Patient." I have deliberately put "The Patient" first and wish in so doing to emphasize that this is as it should be in the practice of medicine. Now, from this much you will see that the patient-physician relationship may be discussed from the collective viewpoint or the personal viewpoint. I shall first speak briefly of the collective public-medical profession relation and then of the personal patient-doctor relation.

I cannot summarize here all of my reasons for being opposed to compulsory health insurance. I think it would be disastrous for our country. I think it would result in a calamitous waste of time and strength of the doctor, a deterioration of medical care, and a ruinous drain upon our taxpaying power already strained to the limit. The people must understand that compulsory health insurance practically means conscription of the medical profession. It certainly will compel the doctor against his will to become a government employee. If that isn't conscription, what is it? The implication as to other professions and occupations must not be overlooked.

Now, I must admit that our profession as an organization has been slow to appreciate that good medical care involves something more than taking care of the individual sick patient. Good medical care involves farsighted preventive medicine, sound diagnosis, good treatment, well-planned rehabilitation, and wise medical social service. Spokesmen for the profession have so often and so passionately denied the charge that medical care in this country was inadequate that until recently they have talked themselves and us into a state of complacent unawareness or disregard of the true state of affairs. Since medical care was "not inadequate," we have done too little or not enough over the years to improve it.

Right now too many people are dissatisfied with the provision of medical care in this country and want to change to a system closely resembling, if not identical to, that now under trial in Great Britain. This desire to change is not altogether due to specious argument and propaganda of our socialist neighbors, but in many instances is based upon honest conviction that the medical profession has failed to do as good a job as it should. After unwise opposition to prepaid medical care plans, we are now pushing them vigorously; after unfortunate, but understandable, delay in apprising the people of America as to our creditable accomplishments, and they are many and great, we are now launched upon a highpowered, expensive campaign of education of the public. Now, I am in favor of voluntary health insurance and group-practice prepayment plans. *I have the utmost confidence that without radical change we can continue to move steadily in the direction of providing good medical care for everyone.* Indeed, as a result of this threat of "State Medicine" we are moving more rapidly in that direction. I am further in favor of a dignified campaign of information, but I submit this campaign alone is too little and may be too late.

What should be done? Well, what do you do when you have a sick patient? You sit down at the bedside and take a history and make a physical examination. This and that are "out of whack" and that and this will fix what is amiss. Why not personify the American people and the medical profession? Why not sit down at the bedside in every city and hamlet in the country, find out what is wrong,

and take the lead in correction? Let us apply the technique of the diagnosis and treatment of the individual case to the collective situation. Once a week at the Colorado General Hospital, internists, orthopedic surgeon, psychiatrist, residents and interns, physical therapist, nurses, and social service workers sit down together to review the "condition" of a particular poliomyelitic patient and the medical care as presently provided in his case. Why not follow the same plan in the present indisposition of the "Provision of Medical Care?" The very best publicity we could get would be to publicize the fact that the medical profession was sitting down with competent, fair-minded, nonmedical citizens to study the "Health Situation" in all particulars in our state, to make recommendations based upon this study, and finally and most importantly to undertake wholeheartedly as a united body to correct them. Let me emphasize this: The best publicity for the medical profession is to do such a good job in providing medical care for all the people that the public we serve will not want to change. The organized medical profession must take the initiative, secure the necessary cooperation from allied agencies, and always itself provide unselfish assistance. The suggestion is not new. The procedure has worked most effectively in other states and should prove effective in this state. Years ago, the American Medical Association should have sponsored and furthered this idea on a national scale. Lest I be misunderstood, I say such a "General Health Assembly," which may be on state-wide or county and city scale, should be undertaken for the prime purpose of finding out what is wrong and correcting it. An important preliminary step is the organization of a permanent General Health Council suitably placed. Improvement in our public relations in my opinion will inevitably follow.

Unfortunately, we have allowed ourselves to be jockeyed into a defensive position. We should never have permitted this matter to degenerate into a battle of propaganda, publicity, and legislative pressures. We are told that the provision of medical care to the American people is inadequate. It is folly to waste time and effort shouting from the housetop that the charge is unjust. The times call for deeds and not words.

So much for this broad public-medical profession relation! I will now discuss with you the personal patient-physician relation. Over the years, many doctors have "taken a crack" at this fundamental relation. I earnestly recommend for your leisure reading the little book "A Doctor Looks at Doctors" by Joseph Collins (Harper and Brothers, publishers, 1927). It won't take you more than half an hour to read it. Keep it at your bedside along with three other little books about the same size, "Medicine in the Out-Patient Department" by Winthrop Wetherbe, Jr. (Paul B. Hoeber, Inc., 1938); "The Care of the Patient" (Harvard University Press, 1927; also J.A.M.A., March 19, 1927, *88:* 877–882); and "Doctor and Patient" (The Macmillan Company, 1930) both of the latter by Francis W. Peabody, Professor of Medicine at Harvard Medical School. When a future of great usefulness lay spread before him, Peabody died all too young. I never knew him, but he died greatly respected and greatly beloved.

The little book by Collins appeals to me particularly, not only because it is well and pungently written but because Collins was a doctor who also had lung

trouble, apparently not tuberculosis but an unfortunately treated postpneumonic empyema.

Now, I can say to you from the bottom of my heart that from that day, now just forty-two years ago when I "busted-up," I have received nothing but sound advice and the greatest kindness from my medical attendants. I also owe a great debt to them for the example they set me of thoughtful patient attention to my real and also to my fancied woes.[2]

In December 1907 when things were not going too well with me and I was woefully depressed, Dr. Edward L. Trudeau of Saranac Lake wrote me a letter which helped me wonderfully. Get the picture! I was just another "lunger" in a village where there were hundreds, just a miserable medical student eating his heart out with bitter disappointment, frustration, and self-pity, and this great physician knew it and came to my help. Here is the letter he wrote me at Christmas of that year.

Saranac Lake
December 23rd
1907

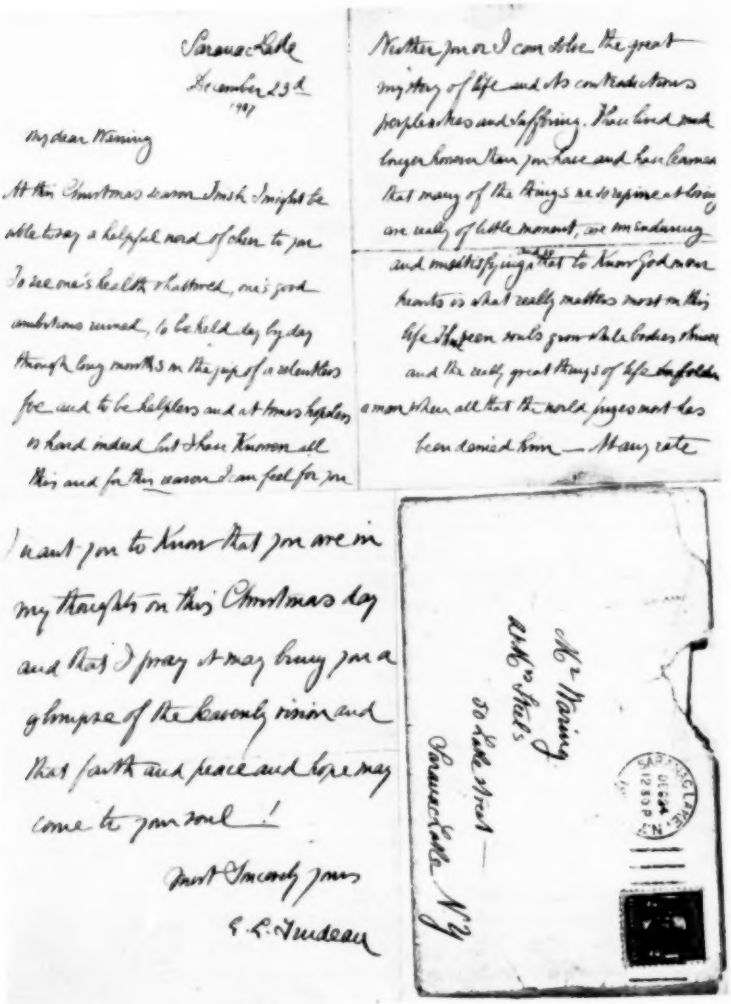
My dear Waring
At this Christmas season I wish I might be able to say a helpful word of cheer to you. To see one's health shattered, one's good ambitions ruined, to be held day by day through long months in the grip of a relentless foe and to be helpless and at times hopeless is hard indeed but I have known all this and for this reason I can feel for you. Neither you or I can solve the great mystery of life and its contradictions, perplexities and suffering. I have lived much longer however than you have and have learned that many of the things we so repine at losing are really of little moment, are unenduring and unsatisfying and that to know God in our hearts is what really matters most in this life. I have seen souls grow while bodies shrivel and the really great things of life unfold to a man when all that the world prizes most has been denied him. At any rate I want you to know that you are in my thoughts on this Christmas day and that I pray it may bring you a glimpse of the heavenly vision and that faith and peace and hope may come to your soul!

Most sincerely yours
E. L. Trudeau

The man and the physician shine in this letter. If I had not had tuberculosis I would have missed knowing this man and having this experience. I would have missed Brown and Baldwin, and Price in the Adirondacks and Webb and Sewall in Colorado and, perhaps, other good friends of my own vintage, to all of whom I owe a debt not easily discharged except at the bedside in a teaching institution.

Doctor Collins was less fortunate. It is worth while reviewing his comments on his experiences as a patient because he seems to have been fair in characterizing the virtues of his medical attendants as well as frank in putting his finger on their shortcomings. From his experience many helpful lessons may be drawn.

[2] Off the record, I wouldn't like to have this generally known, but during the first year of my illness, I was the damndest psychoneurotic that ever took refuge in the Adirondack Mountains.



Saranac Lake
December 23d
1907

My dear Waring

At this Christmas season I wish I might be able to say a helpful word of cheer to you. To see one's health shattered, one's good ambitions ruined, to be held day by day through long months in the grip of a relentless foe, and to be helpless and at times hopeless is hard indeed but I know I know all this and for this reason I am glad for you

Neither you nor I can solve the great mystery of life and its contradictions, perplexities and sufferings. We can find such knowledge now for peace and heart calmness that many of the things we so prize at times are really of little moment, we are endeavoring and must strive that to know God more humbly as that really matters most in this life. Upon souls grow while bodies shrink and the really great things of life unfolded more when all that the world prizes most has been denied him — At any rate

I want you to know that you are in my thoughts on this Christmas day and that I pray it may bring you a glimpse of the heavenly vision and that faith and peace and love may come to your soul!

Most sincerely yours

E. L. Trudeau

Dr. Waring
Care of Mrs
30 Lake Street
Saranac Lake N.Y.

This letter is reproduced through the courtesy of the Transactions of the Association of American Physicians, Philadelphia, 1939.

One doctor of whom he sought advice was:

> a big man with deep chest, soft voice, caressing eye, and gentle touch. His linen was immaculate, his clothing conformed to fashion, and, though he was the busiest doctor in the country, he seemed never to be in a hurry.

A great virtue in a doctor. I know a pediatrician who becomes so absorbed in the problem of one infant and the anxiety of one mother that he becomes completely oblivious of a reception room full of squalling infants and other mothers. How the mothers love such attentiveness!

> He radiated kindliness and sympathy, he reflected interest and concern and he made me feel that my recovery and my future were of vital importance to him.

So much is good but listen to this: "If he made a diagnosis of my disorder he did not tell me." Surely the patient is entitled to a diagnosis. If he does not know what is wrong, he cannot cooperate fully with the doctor for his relief or protect himself later from relapse or recurrence.

Of another doctor Collins consulted he writes:

> He was a deep-chested man too, with a strident voice and keen eye. His *fortiter in re* was genuine; his *suaviter in modo* artificial.

I do not have to translate this Latin to members of the Nu Sigma Nu Fraternity, I am sure. But in case some lost member of a rival organization has strayed into our midst, I hasten to add my interpretation: *his energy was real, his courtesy artificial.*

Collins continued:

> During the eight years I knew him, I heard many flattering things said of him, but I never heard anyone say he was kindly or compassionate. When he died an obituary notice in one of the medical journals said, 'He was an admirable business man.' When one went to consult him, with five dollars, one rang the stoop-door bell; but if one had only a dollar, the basement bell admitted. I went in with the goats.

This doctor without inquiring into ways and means ordered him off to Arizona and Collins had but two dollars in his pocket. The lesson here is so plain that it scarcely needs emphasis. *Never give even the humblest prescription without reasonable assurance that it can and will be filled.* Commenting on this consultation, Collins writes: "That day I determined never on sight to sentence a person for life or to death."

Collins also has a remarkable facility for description. In the following paragraphs he gives in a few words a very clear picture of four physicians to whom he turned at one time or another for help. We might well emulate their virtues and take to heart the lessons of their weaknesses.

Of one physician, Collins says:

> I was impressed with his gentleness, solicitude and attentiveness. He was the most genuine of men, who had laboriously taught himself the science of diagnosis, and whose failure to acquire the art of it was in a measure compensated for by his honesty and optimism.

Of another doctor, Collins writes:

> He was a born diagnostician and something of a wizard as well. He looked the part. But if he had any fellow-feeling for a sufferer he could conceal it better than

> anyone I have known. I think he enjoyed telling me that I was affected with an incurable disease. Fortunately I did not believe him and more than that, both his reception of me and his interpretation of my disorder had angered me. I felt I had not been treated as a human being.

Of still another, Collins says:

> He informed me that he was instructor of physical diagnosis in a well-known university. If automatons could have diseases, I should select him for their physician.

Collins later consulted a friend who was then retiring from the practice of his profession after a brilliant career, "a man of penetrating clinical insight, abundant horse-sense and sound judgment."

I subscribe to Doctor Collins' warning against death sentences. It is so easy to be wrong. Courage and determination often make the difference between victory and defeat in illness. Hope springs eternal and should never be crushed by thoughtless or deliberate word. At the outset of my illness my future evidently looked dim to my friends, for only ten years ago I received a letter from a former medical school classmate, of whom I had heard nothing and who had evidently heard nothing of me since medical school days. He suddenly discovered that I was still alive and wrote me a nice congratulatory letter beginning "Good God, Jim, I thought we had buried you thirty years ago!!"

In the presence of the patient no remark should ever be made that might conceivably add to his anxiety and apprehension. Never forget that he is watching you like a hawk for the slightest sign of hope or hopelessness. Some time ago, I had under my care a good woman with a recurrent cancer of the breast, the recurrence being manifest in spine and peritoneum. Although I gave the family a precise opinion, I always evaded the issue with her. As I sat beside her bed on the day she died, she suddenly reached out her hand and put it on my arm and said: "I am grateful that you would never admit that it had come back."

Another caution! In the presence of the patient restrain all expression of pleasure over some sign or symptom. In the early years of my practice, a brilliant colleague told me sadly that he had just been fired by a prominent family. What happened? The head of the family lay dying of Bright's disease. My friend's unrestrained pleasure over the "beautiful" albuminuric retinitis seen in the eyes of the poor nephritic so offended the family that as he left the house he was told not to come back.

Elation over some interesting pathologic sign or symptom cries to high heaven that you have lost sight of suffering humanity. Pure compassion is ingrained and cannot be taught, but outward expressions that may mean nothing more than thoughtlessness, and not heartlessness can, at least, be controlled.

Collins says physicians are "so prone to occupy themselves with the theoretical requirements of a case that they lose sight entirely of the human being and his life story."

Sadly he comments, "With two exceptions my doctors were not interested

in *me*. They were interested in a morbid condition of my body which was enigmatic to them, and in a repair job of Nature the like of which they had not previously seen."

Collins concludes his little book with these two sentences: "The glories of medical history are the humanized physicians. Science will always fall short; but compassion covereth all."

The inscription on the beautiful monument to Dr. Edward L. Trudeau at Saranac Lake, the great and kindly physician who founded the sanatorium movement in this country, reads as follows:

"To cure sometimes, to relieve often, to comfort always."

REHABILITATION FROM THE STANDPOINT OF THE TUBERCULOSIS PHYSICIAN

STUART WILLIS

All who had the privilege of knowing Dr. E. R. Baldwin appreciated the fact that he manifested keen and intelligent interest in all medical and sociological phases of the patient with tuberculosis. He reckoned the disease as one of serious economic proportions and saw many families disrupted because of its inroads.

From his very early days, he manifested an interest in the rehabilitation of the patient, and it is of interest to note that in the last annual report of the Trudeau Sanatorium and Foundation it is indicated that 148 ex-patients who were working after rehabilitation had earned $209,000 in the year 1948.

Up to the later years of his life, Doctor Baldwin manifested interest in the activities of the Saranac Lake Study and Craft Guild and in 1946 sent the following notation to the secretary of the Guild:

What is Basic for Rehabilitation

1. What is basic in the rehabilitation of all kinds of handicapped people?
   a. That the subject be medically passed for fitness to undertake employment of some kind, including willingness and desire for it.
   b. As applied to tuberculous patients, it should mean ability for four to six hours of occupation without undue fatigue or the return of other symptoms of the disease.
   c. In pulmonary tuberculosis the term of treatment must have been at least six months, before beginning rehabilitation, for all who have had manifest symptoms with sputum positive.*
   d. The selection of the special occupation for the individual should be made only after a psychological and intelligence test.

(Signed) Edward R. Baldwin

* Exceptional cases may have chronic disease, stationary in character, who can be suitable for occupations not involving danger to other persons.
August 7, 1946

These days there are those who will question the wisdom or the propriety of having patients with positive sputum to carry on work, but one will observe that Doctor Baldwin's footnote took that fact into account.

Definitions of rehabilitation are many. At base it embraces those maneuvers which are calculated to improve the patient's chances of recovery and point to gainful occupation after discharge. In rehabilitation the physician has a serious responsibility, quite as serious as that of the rehabilitation worker himself. Unfortunately for the circumstances, too many physicians still regard rehabilitation as another field of endeavor which is only vaguely related to medicine.

The doctor has a unique opportunity of establishing a friendly entente with the patient upon his admission, and of using that friendly understanding to the patient's best interest. He must be leisurely and unhurried with the patient. He must give the patient the impression that it is his job and his pleasure to work along with him. He must tell and retell the patient the art of physical, mental, and

emotional relaxation and must convince the patient that, by learning and applying the philosophy of relaxation, he is contributing to his own recovery. The doctor will soon form a good idea of the patient's prognosis which is basically important in any plan of rehabilitation. The patient must always remember that returning health and efforts in rehabilitation are closely related.

Most sanatoriums make a sincere effort to utilize fully the combined procedures of medicine, surgery, nursing, and dietetics in the treatment of its patients. In these it fails at times but its failures are not nearly so frequent as are its failures to obtain the cooperation of the patient. The sanatorium has lost too often the opportunity to capture the patient's interest or to create in his mind the conviction that he is in a good hospital about which he could become enthusiastic.

Why has failure thus befallen? Too often the patient becomes discouraged at the slow rate with which his disease changes. Frequently he is without relatives or has but few visits from them. In many instances he grows stale, becomes dissatisfied and then unhappy, and (all too often) he defeats himself and the sanatorium by either becoming antagonistic to the sanatorium's efforts or by walking out before his disease is brought under control. At times he needs someone to look after a matter for him; to see about an insurance policy nearing lapse; to inquire concerning the reported illness of some member of his family; to intervene for his dependents in the question of clothing, food, or rent; to help him with his employer about having a job when he recovers, even to write a letter or to make a phone call. Such needs daily come to the staff, and the sanatorium, as a rule, is not well equipped to meet them. But what has this to do with rehabilitation? In reality it has much to do with it, because adequate rehabilitation depends upon good medical support, good social work assistance, good occupational therapy work, and good rehabilitation guidance.

If the doctor does his part in mental conditioning of the patient and social workers try to do their part in resolving the patient's troubles from without, the patient should fare much better than he does now, on the average.

Upon admission the patient is shocked at the diagnosis of a disease that kills many. He is bewildered over the economic effect of his illness on his family and wonders if he himself will survive, or, if he does, will be able to earn a livelihood. Very early in his sanatorium stay he needs information about his disease (which his physician should endeavor to supply) and instruction, often repeated, about his part in his own recovery. He also needs guidance in vocational and rehabilitation matters to give him encouragement to do his part and, early in the treatment, to have him think in terms of reconditioning himself.

How is it best to realize these objectives? The writer believes they may be brought into use by establishing a rehabilitation department in the sanatorium which shall consist of social work, occupational therapy, and rehabilitation counseling. Let us look at these three divisions separately for the moment.

Social work: The mental and emotional status of the patient has already been emphasized, and the need for help in resolving such matters for the patient has been intimated as well. Trained social workers who feel keen sympathy for the patient in his plight and who know the techniques of working through with the

patient and his family to a successful conclusion of the matters which disturb have a real opportunity to be of genuine help. Such a person can be "contact man" for the patient, whether the patient be man, woman, or child. The worker can sit down with the patient often enough and long enough to establish a feeling of confidence, after which the patient will present the problems which are worrying him. Often such a person can get a better line on the patient's problem than can the doctor, and a good, cooperative social worker can do a great deal toward "tipping the doctor off" on the mental and emotional problems which the patient is facing and thus enable the physician to direct his attention particularly to these points. The social worker, as a part of the over-all rehabilitation service, is an important and an essential element.

Occupational therapy: During the inactivity enforced by his illness, the patient needs attention and diversion and, when practicable, he should be guided into ways that might lead to "future economic independence." This sort of therapy should begin at the bedside and may at first be purely diversional, but it tends strongly to make a contented patient. The patient needs the services of a combined rehabilitation-occupational therapy department which could plan and execute diversional and rehabilitation work and direct the interest of the patient into occupational thinking. Tuberculosis is a crippling disease which attacks many people in whom return to their former occupation would be hazardous. With a view to training the mentally qualified patient in one of the limited number of trades or occupations tolerated by people who have had tuberculosis, the department should subject the patients with good prognosis to tests in aptitude, interest, and intelligence. Thus training could be begun in the sanatorium and completed on the outside by the Vocational Training Division of the state government.

Meantime, a considerable number of patients will have that degree of tuberculosis which will prevent their return to gainful occupation. Are they, therefore, to be abandoned? The proper organization should have an occupational therapy department which would give diversional efforts to such patients. All manner of light, harmless and, sometimes, aimless activity could be encouraged. Many patients who are unable to recover fully, and thus to learn a new occupation, may do knitting, model making, fish-fly manufacture, reading, soap carving, drawing, and may engage in almost any diversional effort which would be within their physical limitations. Occupational therapy may also teach some of the crafts, such as leather work, weaving, rag-doll work; all of these to cause the patient to be somewhat more contented in his environment and to take his mind off his rather dismal future.

Rehabilitation counseling: Once the patient is established in the sanatorium and has developed some sort of adjustment to his new life, rehabilitation can actually begin in principle. The patient could be started early in selected reading and bedside work and could be advanced as his disease improved. As a sound basis for his rehabilitation work, however, his prognosis, his aptitudes, interests, and basic intelligence must have been determined accurately. Preliminary rehabilitation work would not lengthen his sanatorium stay. On the contrary, it

would rout discontent so that his rest could be more productive, and at the same time it would give him a long start toward his post-sanatorium rehabilitation work.

To this end the staff of this department would carry a full history of the patient, his education, aptitude, basic intelligence and interests, and notes from the doctor on his prognosis. The staff in the rehabilitation department would hold weekly conferences on patients ready for consideration, just as the sanatorium now conducts conferences on the physical status of the patient. The conference would be conducted by the division director or the rehabilitation counselor. In attendance would be the social worker, the occupational therapist, the rehabilitation worker, all of the working staff, a representative from the State Vocational Department of Rehabilitation, the librarian, and the school teacher. In addition, the doctor whose patients are up for conference would be present. The patient's entire case would come up for deliberation and conference recommendation. Here the general course and policy as to rehabilitation for the patient are determined.

During the patient's sanatorium days, training might be begun in the following occupations:

Watch repairing	Stenography and typewriting
Barber work	Typewriter repair
Photography	Radio repair
Beauty culture	Accounting
	Drafting

It is realized that some people believe that barber and beauty culture work are unsuitable occupations for tuberculous patients because of sanitary reasons and the necessary close contact between operator and customer.

A rehabilitation department of this kind would enable the sanatorium to do a greatly improved job and would contribute unmeasured savings to the community in preventing walkouts by unhappy patients and in a higher proportion of permanent recovery among dischargees.

Physicians have been altogether too slow in assuming their proper place in the rehabilitation efforts of the sanatorium.

BRONCHIAL STENOSIS

EDGAR MAYER AND ISRAEL RAPPAPORT

Bronchial obstruction soon leads to pulmonary complications. Failure of early recognition is often paid for with resection of the lung, either in its entirety or in part. In this era of antibiotic therapy, modern operative bronchoscopy, and advanced thoracic surgery, many lobes or lungs thus sacrificed can be saved by early recognition of bronchial stenosis. This condition still goes all too frequently unrecognized until the later roentgenographic features occur.

Failure to diagnose early bronchial stenosis may frequently be traced to negligent or inadequate performance of auscultation. Too often significant symptoms and physical signs pass unnoticed. In a recently published textbook on chest diseases the coming generation of physicians is advised, surprisingly, to use the stethoscope only to get acquainted with the patient; whereas, for diagnosis the physician is exhorted to rely chiefly on the roentgenogram.

Actually, in the early phases of tracheobronchial disease, little help is obtained from the roentgenogram. Instead, chief reliance must be placed upon auscultation and, for confirmation of diagnosis, on early bronchoscopy. The roentgenogram fails us in early bronchial stenosis; the first indications of bronchial obstruction demonstrable by roentgenography occur almost always after pulmonary complications already have arisen.

Two case histories will be presented here briefly, stressing the practical importance of early diagnosis of bronchial stenosis. In these the value of the localized wheeze and its significance in the diagnosis of bronchopulmonary disease will be demonstrated.

Traumatic bronchial obstruction: In the first case the clinical history emphasizes the great need for early diagnosis of bronchial stenosis. This case represents an unusual form of bronchial obstruction of traumatic origin, which we believe is unique in the literature. A full-length report on this unusual observation is now in preparation. Here we will present in brief some of the highlights, only sufficient to illustrate the essential points.

A 25-year-old robust laborer was buried up to his neck by a landslide which pressed his right chest against a large concrete sewer pipe. He was released rapidly and delivered promptly to a nearby hospital. There he was found to be suffering from mild shock, severe dyspnea, and aphonia. Extensive subcutaneous emphysema developed and rapidly spread over both sides of his chest, neck, face, and arms. Roentgenograms of his chest showed intact rib cage, complete opacity over the right hemithorax, and interstitial emphysema extending from the right lung upward on both sides of the mediastinum into the neck. The physicians who observed him at the hospital diagnosed ruptured trachea (site undetermined), right-sided pleural effusion (probably blood), edema of the larynx causing aphonia, and accumulated air in the tissues around the larynx, causing dyspnea. During the next four weeks roentgenograms showed clearing of the right lung and absorption of the interstitial and subcutaneous emphysema. By the end of one month roentgenographic examination showed both lung fields to be clear except for a slight clouding of the right costophrenic sinus. Only a slight thin airstreak in the left side of the neck remained of the vast amount of subcutaneous emphysema (figures 1a and 1b).

Within four weeks the patient had apparently recovered from all of his injuries and was discharged from the hospital in a satisfactory condition. For the next four weeks he remained at home, ambulant, under observation of a private physician and a board of health chest clinic.

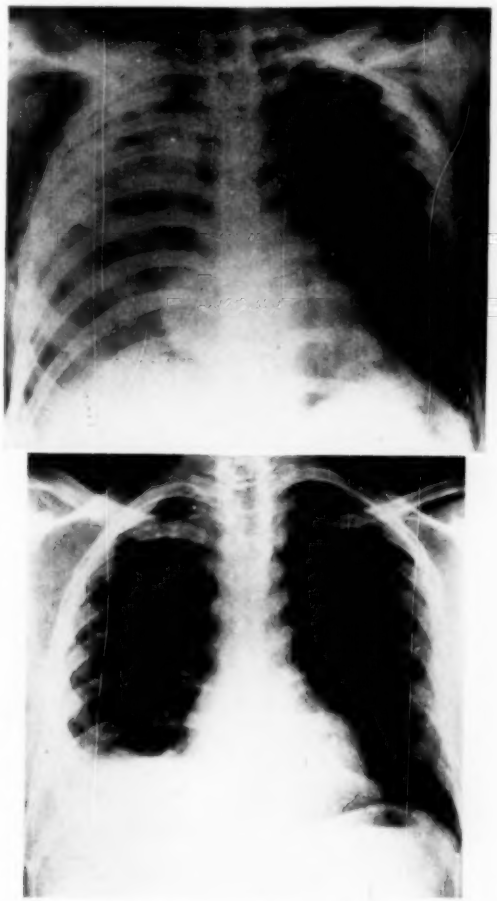


FIG. 1a (Top) Case 1. Chest film on August 1, 1947, three days after trauma.
FIG. 1b. (Bottom) Case 1. Chest film on August 22, 1947, three weeks after trauma.

He came under our observation exactly two months after his accident. By then he complained of a recurrence of dyspnea, pain in the right chest, and a dry hacking cough. We elicited the story that he was *conscious of a wheeze persisting throughout the entire period of his illness*. It gradually grew in intensity and remained present until about two weeks before our consultation, when it suddenly ceased.

Examination revealed massive collapse of the right lung with extreme shift of the trachea, mediastinum, and heart to the right (figure 1c). Bronchoscopy, now done for the first time, revealed complete obliteration of the mouth of the right main bronchus at the level of the bifurcation. The bronchoscopist could not see any trace of the right stem bronchus

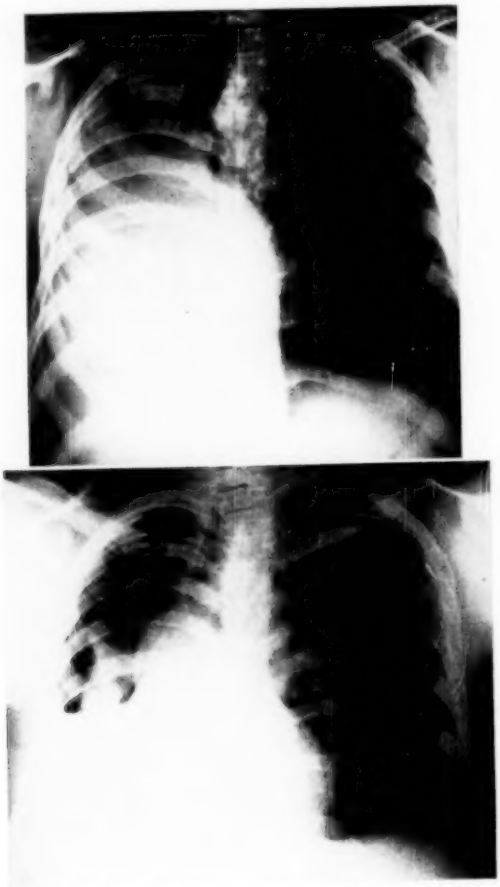


FIG. 1c. (Top) Case 1. Chest film on September 30, 1947, two months after trauma.
FIG. 1d. (Bottom) Case 1. Chest film on November 28, 1947, following air insufflation.

or even a depression to indicate its site. A rubber catheter, passed down the trachea under fluoroscopic guidance, invariably entered the left main bronchus. Lipiodol, instilled into the trachea in all positions, always entered the lumen of the left main bronchus. A second bronchoscopist reported seeing a firm scar to the right of the carina, flush with the tracheal mucosa, which he thought represented the site of the obliterated mouth of the right stem bronchus. Any attempt to reopen a path to the right lung by cautery was deemed too risky.

On induction of pneumothorax (figure 1d) very high negative pressures were recorded and a small amount of clear, straw-colored pleural fluid was obtained. There was no evidence of hemothorax. After consultation with chest surgeons, there appeared to be no other possible treatment short of resection. At operation the surgeon could find no evidence of injury to the right main bronchus. In the resected specimen of the right lung, including a portion of the right main bronchus, examination revealed no evidence of injury and failed to disclose the cause of the massive collapse of the apparently normal right lung.

In this unusual case we are required to explain not only the ultimate collapse but also the atelectasis of the right lung occurring immediately after the trauma. Moreover, there is to be explained the long interval of six weeks during which the lung remained expanded. Space does not permit a full discussion of all the evidence inclining us to our theory on the sequence of events in this case. This will be presented in a forthcoming publication. We assume the occurrence of two distinct traumatic phenomena: (*1*) "blowouts" in the compressed lung leading to extensive interstitial and mediastinal emphysema (1); and (*2*) "blowout" in the tracheobronchial tree (2), with tear at the junction of the trachea and right main bronchus, leading to vast subcutaneous emphysema. The former explains atelectasis developing immediately after the trauma. The second explains the slowly progressive occlusion of the right main bronchus by the granulating tear in the trachea during the six weeks following the trauma. The main point of interest here is that the ultimate collapse of the right lung might have been prevented. Had the progressive bronchial stenosis been recognized at an early stage, it might have been possible to prevent the ultimate occlusion of the bronchus by bronchoscopic interventions or possibly even by surgical intervention dealing directly with the tracheobronchial tear itself.

Bronchial obstruction with a nonopaque foreign body: In the second case, a 50-year-old apparently healthy male developed recurrent attacks of "pneumonia." The first of these occurred in March 1948 and subsequent attacks recurred approximately every six weeks until October 1948 when he came to us complaining of foul expectoration. Two of these attacks of "pneumonia" were treated in a hospital; the others were treated by local physicians employing practically all of the known antibiotics. Repeated roentgenographic examinations failed to reveal the presence of a foreign body.

We elicited a history of persistent wheezing present even before the first attack of pneumonia in March and of recurrent hemoptyses during the past six months. However, the roentgenogram illustrated (figure 2) likewise showed no evidence of a foreign body but suggested a pneumonitis at the left hilum with slight extension into the left lower lobe. On repeated questioning, the patient gave no history of aspiration. Auscultation showed localized wheeze with rhonchi over the left lower lobe.

Bronchoscopy was done now for the first time, and a beef bone was extracted with forceps from the left lower lobe bronchus. The bronchoscope had to be removed to allow the large foreign body to come through the bronchial lumen. Only after the patient had been told of the beef bone in his bronchus did he recall an incident, nearly a year before, in which he "choked" on a piece of meat.

Here again, early diagnosis and early bronchoscopy would certainly have prevented the development of suppurative disease.

In pulmonary tuberculosis also, bronchial involvement leading to bronchial stenosis is overlooked all too frequently with the result that suppurative disease

supervenes. In cases long treated for bronchiectasis, bronchoscopy has often revealed to us benign or even malignant bronchial neoplasms. In all of these, careful auscultation has readily evoked the wheeze; and careful history-taking has demonstrated its persistence for some time.

Many years ago Jackson described "asthmatoid wheeze" as a sign of bronchial obstruction due to a foreign body in the air passages. The growth in significance of this sign in the diagnosis and treatment of bronchopulmonary conditions is now commonly recognized.

In bronchial obstruction due to nonopaque foreign bodies, localized wheeze is the only reliable sign leading to correct diagnosis. It should be recognized that

FIG. 2. Case 2. Chest film on October 19, 1948, at time of bronchoscopy.

there are other important bronchopulmonary diseases in which wheeze, if not the only sign, is often the earliest leading to diagnosis. In some of these, such early diagnosis may be a matter of life or death to the patient. In final analysis, bronchial stenosis is the common denominator of all conditions in which wheezing is heard.

Definition: Jackson originally defined the asthmatoid wheeze as a sound heard by placing the ear in front of the patient's mouth during expiration, resembling the wheezing of an asthmatic patient but drier, and caused by the vibrations of air passing the foreign body in the bronchus.

Although wheezing has been constantly referred to in the vast literature on bronchial stenosis, little attempt has been made thus far to define or even describe it adequately. Among internists practicing auscultation, great confusion prevails

as to the nature of wheezing as an auscultatory sign. Most of them speak of special "wheezing rhonchi" or "rhonchal sounds." Others do not even mention wheezing but include it among the usual rhonchi. Certainly it is not clear from the literature whether a wheeze is a special type of breath sound or an adventitious sound.

More recently another bronchoscopist, Friedberg (3), is more explicit on this question. He defines wheezing as an "altered respiration of asthmatoid type," and concerning its mechanism of production he states: "Pathologic narrowing of the bronchial lumen coupled with physiologic shortening and contraction of bronchi combine to produce abnormal vibration of outgoing air during expiration. The resultant sound is often wheezing in character."

We have come to consider wheeze as an *altered breath sound*. There are great differences in the character of the wheeze in various patients and in the same patient from one time to another. The reason is that the breath sound, like other sounds, may be changed in any or several of its components, namely, quality, intensity, duration, and pitch. The size, thickness, and rigidity of the air passage affected and the degree of stenosis determine the change in the breath sound.

Palpability of wheezes strongly suggests that abnormal vibrations, not only of the air in the bronchus but of the bronchial wall itself, play a role in the production of the altered sound.

Auscultatory signs in obstruction of air passages. Wheezes and rhonchi: Observations lead us to believe that in stenosis of the air passages, certain adventitious sounds, namely, rhonchi of sonorous and/or sibilant type, are usually heard in addition to, and quite distinct from, the wheeze. The rhonchi are probably produced by air vortices at the obstruction due to viscid secretions which usually collect there.

We have noted that a localized wheeze is often mistaken for an adventitious sound when heard against the background of the breath sounds coming from the rest of the lungs. The latter affords a striking contrast to the changed-wheezing-breath sound coming from the affected area.

The auscultatory signs associated with air-passage obstruction are rather complex; they cannot be described merely by the terms wheezing and rhonchi. Each section of the tracheobronchial tree has its own characteristic features. One should begin with the trachea; there the signs have been described repeatedly by Jackson. One need only comment that "stridor" is the most characteristic feature of high air-passage obstruction from the larynx down to the bifurcation of the trachea.

Jackson's scheme of valve-action effect of bronchial obstruction applies chiefly to obstruction by a foreign body in the bronchi. When speaking of bronchial stenosis of other origin, it seems preferable to us simply to grade it as mild, severe, or complete obstruction.

Varying degrees of obstruction of the main bronchi will produce different signs.

Mild obstruction interferes little with the movements of air but already this increases the breathing effort. As inspiration is the more active force, a sharpening, whistling inspiratory sound is often heard as the first indication of a narrow-

ing bronchus. As the obstruction increases, expiration too becomes altered and a transient discrete wheeze makes its first appearance. At this stage the wheeze may be particularly elicited when the patient is lying on the affected side.

As obstruction becomes severe in degree, the wheeze becomes more persistent and less discrete and is heard in both phases of breathing. As viscid secretions accumulate at the point of obstruction, coarse rhonchi, sibilant and sonorous and grunting noises make their appearance. Eventually in severe obstruction, expiration becomes more labored, and as egress of air becomes less than entrance, obstructive emphysema develops. By this time wheezing and rhonchi are constant.

Finally as obstruction grows *complete*, the affected lung becomes increasingly wet with areas of "drowning," leading ultimately to complete atelectatic edema. By now wheezing and rhonchi have ceased. If atelectasis is not relieved, sooner or later it invites infection ending in abscess or bronchiectasis.

The loud stridor of tracheal obstruction gives way to fainter wheezing in central bronchial obstruction and even fainter wheezing in peripheral bronchial obstruction while at the same time the rhonchi becomes increasingly higher in pitch and intensity. In bronchiolar obstruction we hear the very high-pitched, musical, squeaking rales of asthma.

Fluoroscopic sign of bronchial obstruction: The above sequence of events from mild to complete bronchial obstruction can be conveniently followed by roentgenography showing the change from normal to obstructive emphysema to ultimate atelectasis.

However, in the early phase of central bronchial obstruction there is an important fluoroscopic sign which reveals bronchial obstruction even when at times the physical signs are inconclusive. This is the *shifting mediastinum*. During expiration the mediastinum, including heart and trachea, shifts toward the normal side, returning to midposition in inspiration. In bronchial foreign body obstruction in children, one observes on expiration the heart bouncing away from the ballooned lung. This phenomenon is due to the immobility of the affected side, where obstructive emphysema prevails with fixed depressed diaphragm, widened intercostal spaces, fixed ribs, and mediastinum displaced towards the normal side. As the nonobstructed lung expands in inspiration the mediastinum shifts back to midposition; as it contracts in expiration the mediastinum shifts back to its former position. After atelectasis has occurred the mediastinum shifts permanently to the affected side. This shift is enhanced by inspiration, lessened by expiration, and now the movement is towards the affected side.

Symptoms of bronchial obstruction: Cough described as "hacking" is one of the most constant and early symptoms of bronchial obstruction. It is mostly unproductive, yet probably elicited chiefly by secretions accumulating at the narrowed lumen which are difficult to remove.

Dyspnea in the sense of disturbed breathing, a mild sense of suffocation and urge to overbreathe, aggravated by exertion, is one of the most frequent complaints of patients with bronchial stenosis.

Chest discomfort, as a sense of constriction of the chest apart from dyspnea and not influenced by rest or exercise, is also a frequent symptom.

Expectoration, at first thin and scant, then increasingly thick and more profuse and occasionally *blood-tinged*, is a regular feature of bronchial stenosis.

Wheeze, as a subjective complaint, chronic or recurrent and not clearing up after expectorating, may be early or late.

Clinical diseases: The following tabulation indicates the great *variety of conditions in which bronchial obstruction* plays a prominent role in the clinical picture.

Etiology of Bronchial Obstruction

I. *Endobronchial obstructions*
   1. Secretions—inspissated as in postoperative complications
   2. Exudates, blood, other pathologic products broken through from adjacent organs (tumor masses, anthraco-silicotic nodes)
   3. Aspirated matter—stomach content
      foreign bodies

II. *Intramural obstructions*
   1. Growth anomalies—congenital
      postnatal
   2. Specific inflammatory processes—tuberculosis, syphilis
   3. Neoplasms—benign
      malignant
   4. Trauma—fracture, rupture with interstitial emphysema

III. *Extrabronchial obstructions* (extramural compression)
   1. Tuberculous lymph nodes, effusions, Potts' abscess, Hodgkin's and other lymphoblastomas
   2. Neoplasms of the lung, trachea, esophagus, and mediastinal structures
   3. Pulmonary emphysema—bullae, cysts
   4. Cardiovascular conditions—aneurysm, hypertrophy, and dilatation of heart chambers

It is only reasonable, therefore, to expect that bronchial stenosis should be a matter of daily observation in hospital wards. Bronchoscopy, which has now become a daily routine procedure, has been instrumental in making us aware of the frequency and clinical importance of bronchial obstruction. It has also been of enormous help in the diagnosis and treatment of all bronchial diseases.

The above tabulation has not included the intrinsic diseases of the bronchi in which generalized wheezing and its attendant symptoms are significant clinical features, namely, bronchial asthma, allergic bronchitis, and pulmonary emphysema with its attendant bronchorrhea.

In clinical practice we are concerned mostly with the common intrinsic diseases of the bronchi in which localized chronic or recurrent wheezing is a prominent feature. The two diseases to be particularly emphasized are pulmonary tuberculosis and pulmonary neoplasms, which make up the bulk of cases of bronchial stenosis observed in everyday practice.

In tuberculosis, one patient in four has a tracheobronchial involvement. Considering the great number of cases of pulmonary tuberculosis, bronchial stenosis of tuberculous origin is a frequent condition indeed. It is still not sufficiently appreciated that bronchial tuberculosis is often present without roentgenographic evidence of lesion in the lungs. Bronchial involvement may precede obvious

parenchymal lesions, and wheeze may be the first and only sign. Chronic localized wheeze, as the first and only symptom in young female patients, should always make us suspect bronchial tuberculosis first. The wheeze enables us not only to diagnose but also to localize the lesion. In pulmonary tuberculosis, unless tracheobronchial involvement is recognized early and collapse therapy modified accordingly, perhaps with early use of streptomycin, the patients' chances of recovery will be greatly impaired. Wheeze is the sign by which such early diagnosis can be made.

Only bronchoscopy can establish the diagnosis of bronchial tuberculosis with certainty. There are practically no contraindications for bronchoscopy in pulmonary tuberculosis when bronchial involvement is suspected. *Persistent localized wheeze or sputum positive for tubercle bacilli in the absence* of roentgenographic evidence of pulmonary lesion or *sputum positive for tubercle bacilli in spite of effective collapse* are the chief indications for bronchoscopy in pulmonary tuberculosis.

Obstruction due to *bronchogenic carcinoma* is, no doubt, the next most common form of bronchial stenosis. Regarding this the following points bear repeated emphasis.

1. It is still not sufficiently appreciated that in the *early* diagnosis of bronchogenic cancer the roentgenogram is usually of little help.
2. Localized wheeze is present in more than 50 per cent of the cases.
3. Careful auscultation for early signs of bronchial obstruction leads to suspicion and to diagnosis by bronchoscopy in the majority of cases recognized in the operable stage.
4. Bronchoscopy serves to establish the diagnosis in 60 per cent of the cases discovered in the operable stage, either by biopsy or by study of cells in the aspirated material.
5. When the condition is diagnosed by roentgenographic features, in the majority of cases it is already inoperable. Waiting for roentgenographic evidence is often responsible for failure of diagnosis in the operable stage.

SUMMARY

1. Prevention of pulmonary sequelae of bronchial stenosis depends on its recognition in the early stage.
2. For early diagnosis of bronchial stenosis we must rely on detection of persistent localized wheeze and rhonchi.
3. Wheezing is an altered breath sound to be distinguished from the rhonchus, an adventitious sound.
4. The great limitation of roentgenographic examination in the early diagnosis of both tuberculosis and carcinoma of the bronchus has been emphasized.

SUMARIO

La Estenosis Bronquial. Argumento en pro del Diagnóstico Temprano

1. La prevención de las secuelas pulmonares de la estenosis bronquial depende del reconocimiento de ésta en su período incipiente.
2. Para el diagnóstico temprano de la estenosis bronquial tenemos que atenernos al descubrimiento de jadeo localizado y roncos.

3. El jadeo es un ruido respiratorio alterado que hay que distinguir del ronco, ruido adventicio.

4. Recálcase la gran limitación con que tropieza el examen radiográfico en el diagnóstico temprano tanto de la tuberculosis cuanto del carcinoma de los bronquios.

REFERENCES

(1) MACKLIN, M. T., AND MACKLIN, C. C.: Malignant interstitial emphysema of lungs and mediastinum as important occult complication in many respiratory diseases and other conditions; interpretation of clinical literature in light of laboratory experiment, Medicine, 1944, *23*, 281.

(2) HODES, P. J., *et al.*: Traumatic bronchial rupture, Am. J. Roentgenol., 1948, *60*, 449.

(3) FRIEDBERG, S. A.: Bronchoscopy and asthmatoid respiration, J. A. M. A., 1943, *123*, 85.

PRESENT STATUS OF THERAPEUTIC PNEUMOTHORAX

J. N. HAYES[1]

During the nineteen twenties artificial pneumothorax was such a popular method of treating pulmonary tuberculosis that it almost superseded the time-tested principle of rest. In fact, as early as possible after diagnosis of the disease the suggestion of pneumothorax was entertained and sometimes was immediately tried. It produced many successful cures but unfortunately was too frequently accompanied by complications, some of them grave. Empyema, with or without bronchopleural fistula, permanently inexpansible lung, and late relapse after re-expansion of an effective collapse, which had been maintained for three to five years, caused some dampening of the enthusiasm for this treatment. At that time we were so glad to assist in a clinical cure that the using up of functioning respiratory tissue in the lower, relatively normal lobe, as a result of a serous effusion, did not worry us. Recently, with greater interest in pulmonar; function, we have become more concerned with saving all of the good lung tissue that we can, so as to be prepared to treat later progression of the disease. At that time, also, we were not aware of the dangers of giving pneumothorax in the presence of bronchial disease.

In 1932 I reviewed the results of ten years of pneumothorax (1) and, while I was not completely awakened to the dangers of this form of collapse, I certainly became less enthusiastic for it. In fact, I recall that at that period the Saranac Lake group of physicians developed a reputation for being too "conservative." I, myself, think that there may be a danger of our going too far in trying to avoid pneumothorax.

Pleurisy: The greatest gain which has resulted from trying to avoid pneumothorax has been the marked reduction in cases of severe pleurisy, both serous and purulent. The latter has become almost a rarity. I believe that the earlier relative frequency of this complication was the result of beginning pneumothorax when the pulmonary lesion was still an acute tuberculous bronchopneumonia. With bed rest we often see the temperature fall and the film reveal less "inflammatory reaction" around the foci. If, together with this improvement, the cavity is seen to be diminishing in size, by deferring pneumothorax we may be able to avoid it altogether. Or, if the cavity does not close, then after two to six months of bed rest when we do collapse the lung, pleural complications are much less likely to occur. Sometimes the activity of the disease in the better lung requires such a delay. All of us have seen patients who in the beginning we thought would need pneumothorax but, while we waited for the better lung to improve, have so improved in the worse lung that we were eventually able to discard the idea of collapse therapy.

Early abandonment of pneumothorax: Of course, one of our greatest advances has been in the early stopping of pneumothorax when it is evident that a good

[1] Medical Director, Gabriels Sanatorium; Attending Physician, Trudeau Sanatorium.

mechanical collapse cannot be obtained. Before thoracoplasty had attained its present development we had nothing to offer to these patients who were frequently as pleased as we were that the cough and expectoration were reduced and the cavity rendered smaller. Now pneumothorax is considered a tentative procedure. We strive, if possible, for a selective collapse, i.e., one in which the diseased area, usually in the upper lobe, is separated from the chest wall and, preferably, also from the upper mediastinum. This frequently requires an intrathoracic pneumonolysis which we like to have performed during the first month or two of pneumothorax treatment. If there are grave doubts about the possibility of closing the cavity, the pneumothorax is abandoned as quickly as possible if another form of collapse offers a chance of success.

It is necessary to give a word of warning to younger men about a danger of selective collapse. There is a tendency at refills to introduce the needle over the lower half of the thorax. Fluoroscopic observation shows that in many cases, with an effective collapse of the upper half, the lung in the lower half of the thorax lies very close to the chest wall, especially during inspiration. In these cases the needle should be introduced in the upper half of the chest to avoid needle puncture of the lung.

Another advance in pneumothorax therapy stems from the development of greater skill by our thoracic surgeons. Many of us now pay more attention to the late results of re-expanded pneumothorax cases than we formerly did. We believe that some types of disease are better off with permanent collapse. In these we choose thoracoplasty as a primary collapse measure instead of pneumothorax. These include patients in whom the disease is fibrocavernous and also those with quite intense, large, nodular disease localized in the upper third of the lung, even though the cavity may be small and the disease not very toxic.

Bronchial involvement: Finally the influence of bronchial tuberculosis in causing complications of pneumothorax has limited the employment of this treatment. We consider a preliminary bronchoscopy a necessary examination before attempting collapse. If the bronchial disease is ulcerostenotic, it is a definite contraindication to pneumothorax. If, however, thoracoplasty or resection cannot be used at the time, even after streptomycin treatment, pneumothorax may be lifesaving in the severely toxic patient, but in these cases we should not rely on pneumothorax as a permanent measure. When the disease is extensive, we should go on to surgical collapse or resection as soon as possible after the toxic symptoms have subsided following collapse by pneumothorax. Some of these desperately sick patients have a brilliant early improvement from pneumothorax but complications frequently occur later.

If, however, the bronchial disease consists only of localized congestion and if the state of the patient precludes surgical collapse, a course of streptomycin will often make pneumothorax a safe procedure. Before the advent of streptomycin, I have seen such a mild bronchial congestion, localized to the main bronchus or orifice of the upper lobe, go on to involve the lower lobe bronchi with resultant atelectasis and loss of function of a presumably healthy lobe during pneumothorax therapy.

Type and location of cavity: Some features about the cavity have influenced us in our use of pneumothorax. A very large cavity is not often permanently closed by pneumothorax. I generally prefer a Monaldi operation followed by thoracoplasty. When the cavity is close to the margin of the lung, either the thoracic wall, or the mediastinal and, possibly, interlobar boundaries, we believe that pleural complications are more likely to occur than if the cavity is deep in the lung. Until pulmonary resection is less hazardous I believe that we are correct in attacking a basal cavity with a phrenic nerve operation, with or without pneumoperitoneum and, if that fails, then with pneumothorax. Some of these lungs heal without more drastic measures.

Phreniclasis: The phrenic nerve operation has decreased our use of pneumothorax. I prefer it to pneumothorax when the cavity is small, 1 to 2 cm., and the lesion relatively fresh, exudative, limited in amount, usually subapical or in the middle or lower third of the lung. Usually the patient has no toxic symptoms. I usually defer the operation for about two months, during which time the patient feels much improved and the roentgenogram shows less inflammatory reaction, although the cavity is about the same size or slightly smaller. On physiologic grounds the decreased motion of the lung resulting from the phrenic paralysis seems to be indicated. In a critical review one could not be sure that a cure was the result of the operation but many of these cases formerly swelled the good results of pneumothorax.

Pneumoperitoneum: A further restriction of the use of pneumothorax has resulted from the increased use of pneumoperitoneum. Some of the enthusiasts of this treatment now use it in cases which were formerly considered ideal for pneumothorax, namely, persistent cavity in predominantly unilateral disease which is too extensive to expect a cure from bed rest alone. Certainly its few complications favor pneumoperitoneum but its successes are not as frequent as those following pneumothorax.

In some cases, however, pneumoperitoneum has given us a chance to use pneumothorax. These include the patients with markedly toxic disease which is extensive and bilateral and is usually associated with multiple bilateral cavities. Pneumoperitoneum combined with streptomycin-para-aminosalicylic acid therapy has sometimes led to such marked improvement in one lung that the worse lung can sometimes be successfully treated with pneumothorax or thoracoplasty.

In the same way pneumothorax may be used in patients with bilateral disease as a preparation for thoracoplasty. The patient is not in condition for thoracoplasty and the better lung is collapsed by pneumothorax in preparation for a needed thoracoplasty for the worse side, or pneumothorax may prepare the way for thoracoplasty on the same side. A patient was too sick for the operation, yet permanent collapse was considered the better method of treatment. After pneumothorax controlled the fever, thoracoplasty was performed two months later while the lung was under collapse by pneumothorax.

Antimicrobial therapy: Streptomycin has made some changes in the pneumothorax program. I have already mentioned its influence in permitting a safe pneumothorax in mild bronchial disease when only pneumothorax could be con-

sidered and its employment, together with pneumoperitoneum, in the severely sick patient with extensive bilateral disease. We give streptomycin in the early weeks of pneumothorax when we believe that we are forced to use pneumothorax in a febrile toxic patient. It is early to report but I think streptomycin is indicated here, as it is in the very sick patient who undergoes thoracoplasty. All statistics have shown that the first two months of pneumothorax therapy is the period in which pleurisy most frequently develops. It is in the toxic patients that severe pleurisies are likely to occur. So far, with the use of streptomycin we have been avoiding such severe complications. Since the advent of streptomycin I have seen no patient with the acute, febrile, clinically serious type of serous pleurisy accompanying artificial pneumothorax. In two patients with such a pleurisy occurring during treatment of pulmonary tuberculosis without therapeutic pneumothorax, I have been struck by the rapidity and completeness of cure of the pleurisy by the combination of early streptomycin treatment with repeated aspirations of the fluid. I would expect a similar result if the acute febrile pleurisy of artificial pneumothorax were treated early and vigorously. In an article by Hyman and Hoffman (2) on the combination of streptomycin therapy and artificial pneumothorax (before, during, and after the establishment of collapse and often overlapping), the authors do not mention acute serofibrinous pleurisy but do record that no empyema complicated the treatment in 90 cases.

In yet another way pneumothorax may be used with streptomycin as a dual method of treatment. After a course of streptomycin has been followed by marked resolution of disease which originally was exudative, extensive, and frequently bilateral, the disease in one lung may be markedly improved and the other improved but with the cavity still present or invisible. The same strategy applies to the more unilateral case. This may be the ideal time for pneumothorax if the remaining disease does not seem to be so intense that it demands permanent collapse.

It must be evident from some of the indications mentioned that pneumothorax today is frequently tried when no other measure is possible. We should never forget the satisfaction all of us have had with the occasional success in the apparently hopeless patient.

Analysis of five years' experience: The test of one's credo is to record how well one lives up to it. I have reviewed my pneumothorax cases treated during the five-year period 1943–1947 at Gabriels Sanatorium and in private practice in Saranac Lake. The number of patients observed and the number to whom pneumothorax was given are recorded in table 1. Comparable data from Trudeau Sanatorium, where the patients generally have less extensive disease, are also given.

The number of patients under my care receiving pneumothorax was influenced by the character of the disease prevalent in Norwegian Government sailors who were under treatment during 1943–1945. They generally had acute, widespread caseocavernous disease. Of the 42 pneumothorax patients in 1943, 19 were Norwegians; and of the 29 in 1944, 10 were Norwegians.

Of these 129 pneumothorax patients, 92 (72 per cent) had far advanced disease;

34, moderately advanced; and one, minimal disease. Coincident with beginning collapse therapy, 40 had bilateral cavities. Twenty-six of these patients received unilateral pneumothorax and in 14 of them bilateral collapse was established; the contralateral pneumothorax failed in 2 others.

When one tries to treat such severe disease the results are necessarily only fair. Effective collapse was established in 51 patients (5, bilaterally effective). In 57 patients the collapse was noneffective on the initial side, but in 3 of these an effective collapse was obtained on the opposite side. In 18 patients the first collapse failed entirely, although in 3 an effective collapse was obtained on the opposite side.

The period during which these patients were under my observation is not the complete duration of their collapse therapy. In the effectively collapsed group, 5 were observed for less than 6 months after the initial pneumothorax; 28, from 6 to 18 months; 21, from 18 to 36 months. However, those with effective collapse rarely ever develop effusion of any consequence after the sixth month. Of pleurisy

TABLE 1

	WRITER'S CASES			TRUDEAU SANATORIUM		
	Admissions	Artificial Pneumothorax	Per cent	Admissions	Artificial Pneumothorax	Per cent
1943	203	42	20.7	238	15	6.3
1944	209	29	13.9	203	10	5.0
1945	219	23	10.5	180	6	3.3
1946	303	21	7.0	220	6	2.7
1947	221	14	6.3	179	8	4.4
Totals	1,155	129		1,020	45	

with effusion we had 64 cases with slight effusion of no clinical importance (2 during re-expansion); in 7 others a serous effusion needed one or more aspirations and the space became dry, and in 2 others we had mild nontoxic tuberculous empyema. I attribute these low figures to three factors: the preliminary period of bed rest to allow a "cooling off" of the inflammatory process, early pneumonolysis, and early cessation of a noneffective collapse.

The rule of quickly stopping pneumothorax when the collapse is ineffective was, surprisingly, not well followed in this series of 56 noneffective cases. Only 10 pneumothoraces were abandoned within one month and 14 more within another month. Sixteen more pneumothoraces were abandoned between the second and sixth months. Sometimes a fairly good mechanical collapse was continued when the disease was extensive on both sides and there was some hope that with passage of time the disease under collapse might heal. Others appeared to be effective for a while and later a cavity was again seen and in others, probably with bronchial disease, the only reason for classifying them as noneffective was

failure to obtain sputum persistently negative for tubercle bacilli. This group included 7 patients whose pneumothorax was maintained for one to three years but was eventually classified as noneffective. In several instances this prolonged pneumothorax was due to the reluctance of a patient to accept resection or thoracoplasty.

When I analyzed the dates of pneumonolysis I was surprised to see how late some of the adhesions were cut. The delay in some cases was due to an early mild pleural effusion. In others, delay occurred because, in our desire to produce as little collapse as possible, we had not produced early enough collapse and the

TABLE 2

Time of Pneumonolysis

Less than 1 month	16	(2 repeats) (1 open pneumonolysis failed)
1 to 2 months	15	(4 repeats)
2 to 3 months	12	(1 repeat)
3 to 4 months	6	(1 repeat)
4 to 5 months	4	
6 months	1	
2 years	1	
	55	

TABLE 3

Indications for Artificial Pneumothorax

Progressive disease and cavity	31	(hopeless, 6)
Cavity stationary or larger	82	(hopeless, 7)
Preparation for contralateral thoracoplasty	4	
Preparation for immediate ipsilateral thoracoplasty	1	
Sputum positive for tubercle bacilli; (tuberculous bronchiectasis, 2) (diag. artificial pneumothorax for questionable cavity, 1)	3	
Spontaneous pneumothorax (cavity present)	1	
Aspirate effusion to re-expand neglected artificial pneumothorax	1	
Prophylactic; history of relapsing disease; artificial pneumothorax after cavity closed and bronchial disease healed with streptomycin	1	
Stationary disease, cavity absent	1	

surgeon needed more space in which to work. The date of each pneumonolysis after the beginning of pneumothorax is presented in table 2, and the principal indications for pneumothorax in the series as a whole are presented in table 3.

Our patients had a good deal of surgical treatment before, coincident with, and after artificial pneumothorax. The individual procedures are recorded in table 4.

Twenty-three patients had failure of pneumothorax before coming to Gabriels or Saranac Lake. Some form of surgery was later performed on the contralateral side in 26 and on the ipsilateral side in 84.

Nine deaths occurred during residence, and 8 more patients are known to have

died, but this study of types of disease in which we believe pneumothorax is indicated does not include a good follow-up. Of 51 patients with effective pneumothorax, no report could be obtained in late 1949 on 14 in foreign countries and on 4 others in this country. Of the 33 remaining patients, in 15 the lung has been re-expanded and the patients are well and working. Fifteen other patients continue with pneumothorax and are well and many are working. In 2 others the disease was reactivated after re-expansion of the lung; thoracoplasty was performed and they are well and working. One of these patients had had a successful contralateral pneumothorax; the other had had a pneumothorax for tuberculous pneumonia complicated by bronchial disease and empyema. The pulmonary disease reactivated after re-expansion of the lung and thoracoplasty was performed successfully. The last patient, who had advanced bilateral disease, died of cardiac decompensation during successful pneumothorax therapy.

TABLE 4

Surgery Before, With, and After Artificial Pneumothorax

Phrenic operation prior to A. P. (ipsilateral)	44	
(contralateral)	16	
Phrenic operation with A. P. (ipsilateral)	3	
Phrenic operation post A. P. (ipsilateral)	6	
(contralateral)	1	
Thoracoplasty prior to A. P. (contralateral)	1	
Thoracoplasty post A. P. (ipsilateral)	19	(refused, 4)
(contralateral)	4	
Monaldi prior to A. P. (contralateral)	2	
Monaldi with A. P. (contralateral)	1	
Monaldi post A. P. (ipsilateral)	4	
Monaldi post A. P. (contralateral)	2	
Pneumonectomy post A. P.	1	
Lobectomy post A. P.	4	
Extrapleural pneumothorax	1	
Pneumoperitoneum	3	
Paraffin block post A. P. (contralateral)	1	

SUMMARY

Pneumothorax is not employed as much today as formerly. More prolonged bed rest, phrenic nerve operation, pneumoperitoneum, streptomycin, and para-aminosalicylic acid therapy have often favorably affected the disease so that pneumothorax treatment is not necessary. But it is a much safer procedure than earlier studies would indicate. This is probably a result of better choice of patients; a period of prior bed rest sufficiently prolonged to permit a subsidence of the most active inflammation; early pneumonolysis; and early cessation of pneumothorax if effective collapse does not seem possible. Pneumothorax is contraindicated, if other measures are available, in stenosing and ulcerogranulamatous bronchial tuberculosis. When thoracoplasty is possible, and the extent and age of the disease makes one fear exacerbation after re-expansion, a primary thoracoplasty is advised without an attempt at pneumothorax.

SUMARIO

Estado Actual del Neumotórax Terapéutico

El neumotórax no se emplea tanto hoy día como antes. El encamamiento más prolongado, la frenicectomía, el neumoperitoneo, la estreptomicina y la para-aminosalicilicoacidoterapia afectan a menudo favorablemente la dolencia de manera que no resulta necessaria la colapsoterapia. Aun así, es un procedimiento mucho más inocuo que lo indicado por los primeros estudios. Esto proviene probablemente de: la mejor selección de los enfermos, un período previo de reposo en cama, suficientemente prolongado para permitir la atenuación de la inflamación más activa, la neumonolisis temprana, y el cese temprano del neumotórax si no parece posible obtener un aplastamiento eficaz. El neumotórax está contraindicado, si hay otras providencias a mano, en la tuberculosis bronquial estenosante y ulcerogranulomatosa. Si es posible la toracoplastia y la extensión y antigüedad de la enfermedad infunden temor de exacerbaciones consecutivas a la reexpansión, recomiéndase una toracoplastia primaria sin probar el neumotórax.

REFERENCES

(1) Packard, E. N., Hayes, J. N., and Blanchet, S. F.: Artificial Pneumothorax, Philadelphia, Lea & Febiger, 1940.

(2) Hyman, G. A., and Hoffman, S. H.: Ninety consecutive cases of pulmonary tuberculosis treated by a combination of streptomycin and pneumothorax, Am. Rev. Tuberc., 1949, *59*, 539.

CARDIAC SYMPTOMS IN THE TUBERCULOUS PATIENT

DANIEL M. BRUMFIEL

INTRODUCTION

Cardiac symptoms rank high among the causes of human distress. There are few conditions more disturbing than the consciousness, or the fear, of a misbehaving heart. In individuals already invalided with chronic disease such as tuberculosis, in which their very physical inactivity renders them sharply aware of all bodily processes, subjective abnormalities take on added significance and frequently become the source of major annoyances or even real anxiety states.

We accomplish little by simply telling the patient to lie in bed and relax. This he cannot do if he is annoyed by symptoms which, rightly or wrongly, he believes indicate a cardiac disorder, or if he is preoccupied by concern about his cardiovascular status. Proper mental relaxation cannot be achieved under such circumstances. Experience has taught us that most of these distressing symptoms are either functional cardiac disorders or of noncardiac origin. But the patient makes no such distinction. For his peace of mind and bodily comfort we must analyze each individual case to determine the real source of his symptoms and then institute appropriate measures for relief.

Cardiac symptoms (the term is used comprehensively to include all symptoms believed by the patient to pertain to his heart) may not occur in the majority of tuberculosis patients. They do occur, however, in a sufficiently large minority to warrant our careful study and management.

The problem of the coincidence of pulmonary tuberculosis and cardiac symptomatology and/or demonstrable physical signs begins at the time of diagnosis. One thousand consecutive first admissions to Trudeau Sanatorium[1] (Cases 6501 to 7500, inclusive) were analyzed from this point of view. Trudeau Sanatorium patients were selected because the criteria for admission automatically limited the subjects to a somewhat comparable group. The very circumstance that they were referred to Trudeau establishes the fact that some competent medical opinion had diagnosed or suspected them of being tuberculous. Few, if any, were admitted in an acute toxic stage requiring nursing care, and in only a comparatively small percentage were the tuberculous lesions far advanced.

ANALYSIS OF CASES

Trudeau Series

The classification of these cases according to the American Sanatorium criteria is shown in table 1. This is the admission classification and has no reference to subsequent clinical progress.

These case records were reviewed with two points in mind: (*1*) a survey of those presenting symptoms which might be related to either the cardiovascular

[1] Through the courtesy of the late Dr. Fred H. Heise, then medical director of the Trudeau Sanatorium.

system or to the pulmonary disease and which might enter into the differential diagnosis; and (*2*) to try to estimate, from the recorded physical findings, the

TABLE 1

Classification of Tuberculous Patients on Admission to Sanatorium

	NUMBER	PER CENT
Minimal	160	16.0
Moderately advanced	588	58.8
Far advanced	166	16.6
Suspected tuberculous	36	3.6
Nontuberculous	50	5.0
Total	1,000	100.0

TABLE 2

Cardiac Symptoms in 1,000 Consecutive Cases

	CASES	PER CENT
Dyspnea	303	30.3
Palpitation	194	19.4
Edema of lower extremities	29	2.9
Left chest pain	20	2.0
Fast pulse	8	0.8
Irregular heart action	6	0.6
History of known heart disease	6	0.6

TABLE 3

Cardiovascular Findings in 1,000 Consecutive Cases

	NUMBER	PER CENT
Number of individuals with murmurs	94	9.4
Judged to be purely functional	75	7.5
Probably organic in origin	19	1.9
With diastolic murmurs	12	1.2
Number with tachycardia (resting pulse rate of 100 or more)	102	10.2
Number with arrhythmia	15	1.5
Number with hypertension (diastolic pressure of 90 or more)	8	0.8
Number with demonstrable cardiac hypertrophy	4	0.4
Number with demonstrable organic heart disease, exclusive of hypertension	12	1.2

incidence of organic cardiovascular disease among such a group of individuals. Attention was limited exclusively to the condition of the patients at the time of admission. The symptoms considered were those given by the patients at the

time the histories were taken, and tabulation of physical signs was made from records of the resident physician who performed the first physical examination.

The symptoms are recorded in table 2.

Dyspnea, palpitation, chest pain, and tachycardia may each, or all, be due to active pulmonary infection. With equal likelihood they may be the manifestation of organic cardiovascular disease. Likewise, such symptoms may be purely functional in asthenic or neurasthenic states, or may be due to any general debility.

Six patients gave a history of pre-existing heart disease. Three were acute rheumatic fever victims, one had had chorea, one had experienced postdiphtheritic myocarditis, and one had suffered an acute cardiac dilatation, cause unknown.

The physical findings upon admission to the sanatorium are presented in table 3.

Systolic murmurs were heard fifty times over the apex and only twenty-three times over the pulmonic area, a ratio which we would expect to find reversed among very ill patients or those with more extensive pulmonary disease. The 10 per cent incidence of tachycardia should be interpreted with some caution because many persons are nervous when first examined in a new institution and by a strange physician. Two of these patients with tachycardia also had histories of hyperthyroidism. The low incidence of hypertension is readily explained by the youth of the patients; only 90 individuals of the entire 1,000 had attained 40 years of age.

Far more important to the patient, and therefore to his physician, are the symptoms which occur in the course of, or following, the treatment period of the tuberculosis. These fall roughly into three etiological groups: (*1*) symptoms purely coincidental and completely unrelated to the pulmonary disease, for example, angina pectoris and coronary occlusion; (*2*) symptom complexes arising wholly or in part as a result of the pulmonary disease. These in turn may arise:

(a) in tuberculous lesions of the cardiovascular system, as pericarditis;

(b) as the result of altered intrathoracic relations, as in acute mediastinal displacement by fluid, air, or massive atelectasis, or as the result of chronic distortion of the mediastinal structures;

(c) in right-sided heart failure due to extensive replacement of pulmonary tissue by fibrosis and emphysema; and

(d) in functional disturbances corresponding to a mild "effort syndrome"-like complex occasionally observed in the toxic stages of the disease, or during the early phases of physical rehabilitation after the disease has become quiescent;

(*3*) symptoms of organic cardiovascular origin but aggravated by the presence, or by the more remote results, of the pulmonary infection, such as intensification of the symptoms of rheumatic heart disease, or hypertension, in progressively active tuberculosis with fever and severe cough.

WRITER'S SERIES

For some years the writer has made a point of indexing all patients seen in his private practice who present any combination of pulmonary tuberculosis and

cardiac findings. From the tuberculosis aspect this has included not only active cases under treatment but patients with arrested disease who have been left with significant residuals such as extensive fibrosis, thickened pleura, surgical collapse and, particularily, chronic distortion of the mediastinum. From the cardiac aspect patients were included who showed demonstrable cardiovascular disease, whether symptomatic or asymptomatic, as well as all patients presenting functional cardiac disturbances. Tables 4 and 5 present the analysis of the 220 consecutive cases indexed as "Heart and Tuberculosis" over a period of several years ending January 1, 1948. It is assumed that these analyses may fairly represent the incidence of various forms of cardiovascular disease (table 4) and the incidence of the various subjective symptoms (table 5) in any comparable group of individuals.

This table illustrates the fact that almost any known form of disease of the cardiovascular system may coexist with pulmonary tuberculosis. Each of these

TABLE 4

Incidence of Organic Heart Disease in 220 Cases Listed as "Heart and Tuberculosis"

Hypertension		35
Arteriosclerosis		10
Coronary occlusion		10
Coronary artery disease (angina)		6
*Rheumatic heart disease		14
Involving aortic valve	4	
Involving mitral valve	4	
Involving mitral and aortic valve	4	
History (valvular lesion not recognized)	2	
Cerebral hemorrhage		6
Syphilitic myocarditis		2
Pericarditis (tuberculous)		2
Total		85

* One of these patients died of acute *Streptococcus viridans* endocarditis.

conditions is potentially symptomatic and must of necessity be properly recognized, or excluded, in any critical consideration of the patient's complaints.

Some of the items warrant further discussion. Hypertension, for instance, may be both benign and asymptomatic or, as is shown in several instances in this list, truly malignant. The tabulation also includes 10 cases of coronary occlusion and 6 of coronary artery disease. Obviously, the 10 individuals who suffered occlusion also had disease of the coronary arteries, but the 6 were patients with true angina who did not develop infarcts while under observation. These same 6 appear also as angina cases in the list of symptoms in table 5. The possibility of coronary occlusion should be kept in mind in all instances of acute chest pain, especially if dyspnea is present, as the pain has been confused with that due to acute pleurisy or spontaneous pneumothorax. During one week three acute myocardial infarctions (not included in this list) occurred among World War I veterans who were under treatment for tuberculosis in the Veterans Administration Hospital at Sunmount, New York.

The incidence of tuberculosis of the pericardium would seem low in comparison with the published necropsy statistics. However, there were only 2 cases recognized clinically in this group. Other than pericarditis, tuberculosis of the cardiovascular system is so rare as to be of academic interest only. The author also has seen, in consultation, one case of tuberculous endocarditis, diagnosed at necropsy.

An attempt has been made to classify the most prominent symptoms or symptom complexes in table 5. In most individuals no one symptom appears alone, although occasionally such may occur. The term "symptomatic cardiac insufficiency" used in the table may need explanation. It is used to indicate a frequently observed syndrome of subjective experience in which there are no objective signs of either right or left myocardial failure. While it is characteristic of lowered cardiac reserve in organic heart disease, it also is common as a purely functional phenomenon. The patient with this syndrome has dyspnea in excess of that to be expected from the amount of pulmonary tissue lost, accompanied

TABLE 5

Incidence of Symptoms in 220 Cases Listed as "Heart and Tuberculosis"

Symptomatic cardiac insufficiency		48
Subjective arrhythmia		61
Premature contractions	36	
Paroxysmal tachycardia	15	
Auricular fibrillation	10	
Paroxysmal	3	
Chronic	7	
Anginoid pain		9
True angina	6	
Pseudo angina	3	
Symptoms of cardiac decompensation		43

by tachycardia, weakness, and palpitation, either with or without subjective arrhythmia.

At least one instance of paroxysmal auricular fibrillation was thought to be functional, although there was a history of probable rheumatic fever. For several months after the institution of therapeutic pneumothorax a transient episode of fibrillation followed each refill.

The question may be raised as to why congestive heart failure is listed among symptomatology rather than organic heart disease. This is done because of the rather typical symptom complex which distresses the patient and for which he asks relief. He is concerned about the swelling of his ankles and is distressed beyond belief by his orthopnea. Right-sided heart failure is an all too common eventuality among persons with extensive pulmonary fibrosis and emphysema. It also has been seen in patients with marked distortion of the mediastinum in whom cardiac pathology could not be demonstrated clinically or at post-mortem examination.

In a separate category, not fitting into the tabular classification, were the 85 cases of chronic distortion of the mediastinum and its contents. Of the total number, 65 had complaints referable to the circulatory system and 20 were symp-

tom free. Several of the 65 with symptoms had concurrent cardiovascular disease but in the majority no cause other than the intrathoracic deformity could be found. The most frequent complaints fell into the "symptomatic cardiac insufficiency" syndrome, about equally divided as to the presence of arrhythmia. This complex was accompanied by an anginal factor in a few cases, and in a very few the anginoid syndrome appeared alone.

Fortunately the incidence of severe degrees of permanent distortion of the mediastinum is on the wane. The more discriminating application of pneumothorax treatment and its prompt discontinuance in the unsuccessful cases will save many persons from this complication. Earlier thoracoplasties, pulmonary decortication of cases of thickened visceral pleurae, and adequate collapse of the chest wall after resections will all tend to prevent this most undesirable aftermath of tuberculosis.

A single instance of an alarming acute cardiac dilatation occurred in a young woman who suffered a spontaneous collapse of the lung in the course of pneumothorax therapy. She made an uneventful recovery. Neither before nor after the acute dilatation was any evidence of organic heart disease found.

COMMENT

No rules can be laid down for the treatment of cardiac symptoms when they occur in the tuberculous patient. Each case must be painstakingly individualized. Once the origin of the symptoms has been determined, standard remedies should be applied. Of equal or even greater importance are the personal interviews for reassurance and explanation of the symptoms. All time devoted to these interviews is well spent. The explanations should be as detailed and as searching as is compatible with the intellectual grasp and insight of the patient. Many of the functional disturbances can be reduced by very mild sedation. This is true of the subjective extrasystoles. In the writer's experience, sedation has been more effective than digitalis in lowering functional tachycardia, an observation which may be of some value in helping to determine whether it is of cardiac or extracardiac origin.

In the days when the therapy of tuberculosis consisted of bed rest only, the physician had no choice but "to treat the patient." The literature of that earlier period was largely devoted to recommendations for control of symptoms to produce that relaxation of body and mind so necessary to recovery. With the great advances which have added collapse therapy, surgical resection, and antibiotics to our procedures, the emphasis has inevitably shifted. By these newer and definitive methods our attention is now focused on treatment of the disease. If we are to achieve our aims, the restoration of the separate individuals to permanent health and to their full degree of rehabilitation, we must redirect our emphasis to the treatment of individual sick people rather than the treatment of cases of tuberculosis. Many of these sick people will have heart symptoms, together with their other complaints. We must recognize these, evaluate them, and do what we can to relieve them while we are applying the definitive measures to control or eradicate the disease.

INAUGURATION OF THE EDWARD L. TRUDEAU FOUNDATION AND THE TRUDEAU SCHOOL OF TUBERCULOSIS

ROY DAYTON[1]

Among the accomplishments of Edward Robinson Baldwin in the fifty-five years of his service to the antituberculosis cause, two achievements were destined to have widespread and continuing influence on the study and control of the disease. These were the establishment of the Trudeau School of Tuberculosis for the teaching of physicians, and the inauguration of the Edward L. Trudeau Foundation, which for the first time placed laboratory research and study by the Trudeau group on a firm financial basis. These enterprises were brought to successful culmination during the busiest period of Doctor Baldwin's life, a time of extraordinary and diverse activities, which followed the death of Edward Livingston Trudeau in November 1915.

As vice-president of the board of trustees and chairman of the executive committee, Doctor Baldwin was the executive officer of the Adirondack Cottage Sanitarium, later Trudeau Sanatorium, on the eve of its greatest physical expansion, when the building of new cottages, an infirmary, and a laboratory increased the patient population by 50 per cent and added greatly to the medical facilities. The tragic death of Theodore B. Sachs of Chicago had elevated Doctor Baldwin from vice-president to the presidency of the National Tuberculosis Association, a position which he took most seriously. Together with Allen K. Krause, H. R. M. Landis, Paul Lewis, and others, he planned and brought to publication THE AMERICAN REVIEW OF TUBERCULOSIS, of which he was the first editor-in-chief. He was director of the Saranac Laboratory, president of the General Hospital and of the Reception Hospital, and active in many other local organizations. It was characteristic of him that he never accepted obligations such as these without giving fully of his time and strength to discharge them, so it may be seen that he carried a heavy load of responsibility through these years.

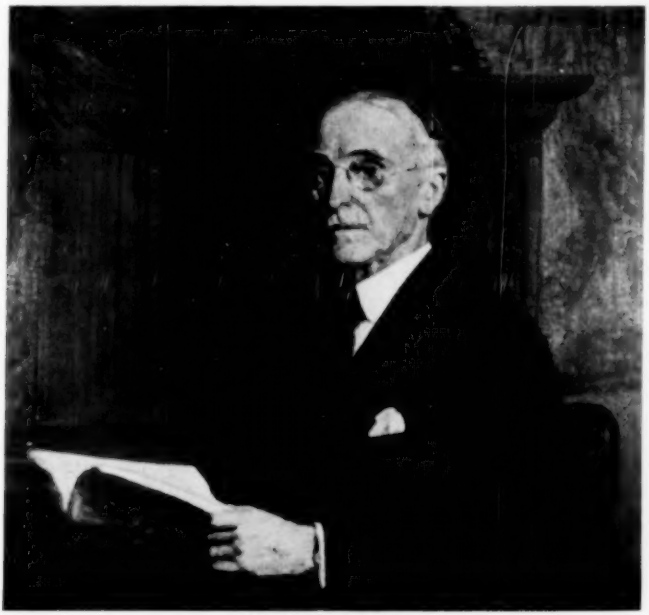
By 1915–1916 the research and clinical experience of the previous decade had resulted in a changing point of view in the concept of the causes of tuberculosis. The doctrines of Cornet and Flügge that inhalation of dust or droplets laden with tubercle bacilli produced all or most of the tuberculous disease in the world were giving way to an appreciation of the universality of tuberculous infection. In the words of Krause (1), the "increasing information of the factors that convert this infection into disease" had given rise to

> a stronger and stronger feeling that in the last analysis the practical fight against tuberculosis must be along broader lines than those which are purely medical. . . . . For many years practically all of the money that was applied to the campaign against tuberculosis was directed to the establishment of sanatoria for the sick. This was only natural before we recognized as we do today that most of us are potentially tuberculous and that

[1] Mr. Dayton became Doctor Baldwin's personal secretary on September 1, 1916 and has been secretary of the Trudeau Foundation and Trudeau School of Tuberculosis since that time.

relapse is as striking a feature of the disease as its tendency to arrest under the proper conditions. But as our realization of the limitations as well as the undoubted value of sanatorium treatment in its effect on the ultimate conquest of tuberculosis has taken definite form, we find that there is an increasing tendency to supplement this expenditure of money for sanatoria with grants to what may more properly be called the pure study of tuberculosis.

Much "pure study of tuberculosis" had been carried on in the Saranac Laboratory by Trudeau, Baldwin, P. A. Levene, Krause, Kingborn, and others, most



Edward R. Baldwin
1864-1947

of whom were volunteer workers. Mrs. Elizabeth Milbank Anderson was giving $5,000 a year to support the work and this, together with occasional small donations from others, constituted the only funds available for laboratory experimentation.

At the Sanatorium, medical research under Dr. Lawrason Brown had received an impetus in 1910 when Mrs. E. H. Harriman established, by a gift of $25,000, the E. H. Harriman Medical and Research Fund; and in 1911–1912 the Olivia Sage Research Fund of $50,000, given by Mrs. Russell Sage, provided further support for investigations. At the time of Doctor Trudeau's death, the income from these funds, which amounted to about $3,300 annually, and Mrs. Anderson's

three-year pledge of $5,000 were the sole assured support of research in the Sanatorium and at Saranac Lake. As a matter of fact, while these contributions were exceeded by later gifts, they constitute convincing evidence of the generosity of the donors and the vision with which they saw the need for a broader attack upon tuberculosis. The gifts were the very first in any substantial amount received by Trudeau for the support of the laboratory and research approach to the problem as distinguished from the purely clinical.

Doctor Baldwin foresaw, with an eye that never overlooked the realities of any situation, that a much larger assured income would be required if extensive and continuous research on tuberculosis was to be made possible at Saranac Lake. Concerned over the paucity of the financial resources available at a time when laboratory investigation began to be a *sine qua non* of the campaign against tuberculosis, he conceived the idea that a relatively large capital fund might be subscribed by friends of Edward L. Trudeau as a memorial to him, the income of which should foster what was, in the words of Krause (1), "the pure study of tuberculosis" and the support of physicians engaged therein. Probably no undertaking of Doctor Baldwin's career was carried out with more singleness of mind and strength of purpose. He laid his plan before the Sanatorium's board of trustees and consulted many leaders in the field, including Charles J. Hatfield, later director of the great Henry Phipps Institute. Doctor Hatfield writes (2): "He spoke to me often of his plan to establish the Trudeau Foundation, which appealed to me, but my help was only prompt agreement in what Doctor Baldwin outlined!" Others with whom he conferred, and who became the Foundation's first advisory council, were William H. Welch, Hermann M. Biggs, William H. Park, Theobald Smith, Warfield T. Longcope, Theodore C. Janeway, and John H. Lowman, all of whom concurred in the plan. The interest of this group provided a strong background of scientific opinion favorable to the Foundation idea.

The trustees of the Sanatorium were enthusiastic. Doctor Walter B. James, Professor of Medicine at the College of Physicians and Surgeons, Columbia University, had succeeded Doctor Trudeau as president. George S. Brewster was treasurer. Other trustees were Charles M. Lea, Edmund Penfold, Stephen Baker, James R. Sheffield, Ogden M. Reid, Harold P. Stokes, Dr. James Alexander Miller, Dr. Lawrason Brown, and Doctor Baldwin. Each one gave time and enthusiasm to the money raising, Doctor James and Doctor Baldwin acting as co-chairmen. The prospectus which was drawn up so clearly reflected the ideal which stimulated the Foundation idea that the objectives set forth therein are quoted in full here:

> The purposes of the Edward L. Trudeau Foundation are:
>
> 1. To maintain laboratories and carry on research into the nature, causes and treatment of tuberculosis, with the ultimate object of discovering a cure, thus continuing what was, after all, the main purpose of Doctor Trudeau's life.
>
> 2. To maintain regular courses of instruction for physicians and others in the most advanced knowledge of the above branches, as well as in the principles of sanatorium construction and management, social service and the relation of the disease to Public Health.

3. To offer to young physicians the opportunity to engage in research work, while undergoing treatment for the disease.

In order to carry out the plan that is outlined above and complete the work that Doctor Trudeau began, at least twenty-five thousand dollars a year is needed, and it is hoped that a fund can be raised, the income of which will be equal to that amount.

This fund will be an enduring monument to Doctor Trudeau. It will be in the hands of the Trustees of the Adirondack Cottage Sanitarium, and will be known as 'The Edward L. Trudeau Foundation.' It will make permanent the work that lay closest to his heart.

The appeal met generous and immediate response. Many contributions were offered contingent upon similar pledges from others. Mrs. Robert Woods Bliss stimulated the campaign by pledging $100,000. George S. Brewster, Mrs. E. H. Harriman, Arthur Curtiss James, Mrs. Walter B. James, Harry Payne Whitney, and William Rockefeller gave or pledged substantial amounts. Many of Doctor Baldwin's own patients contributed.

The goal had been set at half a million dollars, and within five months $257,507 had been received. Public announcement that the Edward L. Trudeau Foundation had become a reality was made at the opening of the first session of the Trudeau School of Tuberculosis on May 17, 1916, when Doctor James said, with an optimism later justified by the event, that the goal of $500,000 would unquestionably be reached. "Up to the present time," he said (3) "the contributions have come with the greatest willingness. I do not believe that any other great enterprise can boast of so large a sum of money that has come so easily. Most of it has been secured by pleasant chats over a cup of tea. And I must say that Doctor Baldwin has drunk more tea than I have." Accretions to the fund were received for several years after this occasion and in 1919 had reached a total of slightly more than $400,000. Meanwhile the $5,000 annual gift begun by Mrs. Elizabeth Milbank Anderson was continued by the Milbank Memorial Fund set up under the terms of her will, and a few years later the annuity was capitalized by an outright gift of $100,000 to the Foundation, when the ultimate goal of a half million dollar endowment was considerably exceeded.[2]

It is beyond doubt that this remarkable achievement could never have had the success recorded but for the magic of Edward Livingston Trudeau's name and the leadership for which it stood in the study and treatment of tuberculosis. It is equally true that the fund could not have been secured but for the confidence which the donors felt in the capacity and ability of Trudeau's assistants

[2] During the depression the securities held in the fund were written down to correspond to the market realties of the times, and at Doctor Baldwin's death the total investments were valued at approximately $490,000. He lived to see the Foundation become the recipient of many research grants, from private and public sources, given for the prosecution of special or general research investigation. These amounted in 1947 to approximately $173,000, which may perhaps be taken as a mark of confidence inspired by the work begun by Trudeau and carried on by Baldwin and Dr. Leroy U. Gardner. After the sudden death of the latter, Dr. Edward N. Packard, medical director of the Sanatorium, was asked to assume also the Foundation leadership and carried on until March of 1947 when Dr. Arthur J. Vorwald took charge of the rearch work, later receiving the appointment as director of the Foundation. Disbursements by the Trudeau Foundation for research and teaching, exclusive of the cost of buildings, reached a total of $1,732,492 for the years 1916–1948.

wisely to direct and carry on the research work which was the purpose of the fund, a confidence stemming partly from the elder Trudeau's estimation of the younger men around him but also from the reputations these men had already made for themselves under his guidance. He once told a friend "Doctor Baldwin has been my best assistant."[3] It is therefore not surprising that upon the shoulders of this "best assistant" fell the mantle of investigative research and that he was from the first the director of the Edward L. Trudeau Foundation until, at the age of seventy-three, he relinquished the task to Dr. Leroy U. Gardner, an early beneficiary of the fellowships supported by the Foundation.

This is not the place to evaluate the contribution of the Trudeau Foundation to tuberculosis study and control, nor is such an evaluation within the province of a layman. However, in passing, it may be noted that one phase of the work, a phase which engaged Doctor Baldwin's abiding interest, i.e., the system of fellowships by which young physicians recovering from tuberculosis were supported while engaged on some research problem, stimulated many workers to careers that have justified the plan a hundred fold. Among the early fellowships which may be mentioned, three were granted to a group who began their service within a few months of each other in 1917–1918. The first was Dr. Esmond R. Long, now director of the Henry Phipps Institute and of the tuberculosis research projects of the National Tuberculosis Association. Dr. Leroy U. Gardner[4] received his appointment six months later and remained with the Foundation to become in 1937 its director and to achieve wide recognition as an authority on industrial diseases as they affect tuberculosis. In the same year Dr. Henry Stuart Willis, then a medical student, worked as a Fellow on his first tuberculosis problem. He is now superintendent of the North Carolina Sanatorium for Tuberculosis. There were many other Fellows who studied under Doctor Baldwin and made their mark in medicine, such as David T. Smith, John B. Barnwell, Cornelius P. Rhoads, Sidney Shipman, Walsh McDermott, David A. Cooper, Gordon M. Meade, Henry W. Leetch, Julius L. Wilson, and others. Just as Baldwin grasped the torch when it fell from Trudeau's hands, so these younger men have picked it up and carried it measurably further toward the goal.

The Trudeau School of Tuberculosis

The Trudeau School, the idea of which had been under consideration for several years, was planned and developed simultaneously with Doctor Baldwin's preoccupation with fund raising for the Trudeau Foundation. Up to 1915 tuberculosis had occupied little part in the curricula of the country's medical schools, and there were few physicians who knew much of the disease unless their own illness or that of some family member induced them to a special study. Tuberculosis had come to be considered as a province apart in the field of medicine,

[3] Doctor Baldwin had published sixty-one scientific papers while Doctor Trudeau was still alive.

[4] Died October 24, 1946.

virtually ignored or inadequately taught. It was difficult for most physicians to learn much about tuberculosis except in sanatorium centers, and material rewards from the care of patients with the disease were meager. Many had come to Saranac Lake to observe Trudeau's methods of treatment and absorb such knowledge as was possible from a longer or shorter association with physicians in the work. Others, received as patients with tuberculosis, passed through the period of treatment and temporary appointments to the staff, recovered, and became "alumni" qualified by a new knowledge with which to cope with tuberculosis in institutional or private practice. But the total of these failed to meet the increasing urgency for specialists in the field.

Perhaps the most impelling need for physicians qualified to diagnose and treat tuberculosis arose from the rapidly expanding number of tuberculosis agencies, due primarily to the publicity campaigns of the National Tuberculosis Association. In 1904 there had been a little over two hundred such agencies in the United States; in 1911 there were fifteen hundred (4) and the number was still increasing. This startling growth had far outrun the number of physicians with proper experience to shoulder the new responsibilities. To those in the work and to others observing the trend it seemed that a short but intensive course of instruction would be of help in meeting the demands.

Teaching, informal or otherwise, had been part of the work at Saranac and Trudeau for many years, as physicians and laboratory workers came from near and distant places to learn something of the Trudeau procedures. The laboratories, clinic, and sanatorium had facilities for such instruction; to present a formal course required only that they be organized and that funds be available to meet the expenses of the new undertaking. The plan had been discussed at various times prior to Doctor Trudeau's death. It engaged his continuing interest and approval, and yet with characteristic modesty he hesitated to promote a school for "teaching advanced knowledge of tuberculosis" when, as he thought, so many universities were in a position to offer such courses if they only would. Baldwin, Brown, Kinghorn, and others of the younger men took a practical view of the problem, arguing that, since there was no postgraduate teaching in tuberculosis and since there was a real need for such teaching, a school should be instituted as soon as possible.

Increasing pressure on the Sanatorium for trained men to take other positions finally convinced Doctor Trudeau that his young associates were right but, when in 1915 he at last conceded the necessity, he maintained (and this is further testimony to the modesty which marked his entire life) that his name should not be used in connection with the proposed school.

There remained the necessity of financing the project.

About this time Dr. Robert H. Bishop, later Commissioner of Health for Cleveland, Ohio, came to Saranac Lake to acquire information useful in developing the municipal sanatorium then planned by Cleveland health authorities. He was impressed with the facilities for study, with the group of clinicians and research workers surrounding Trudeau, and by the amount of clinical material in Saranac Lake and in the sanatoriums which had grown up around Trudeau. He

believed that funds could be found to support a teaching institution. Under the stimulus of Doctor Bishop's enthusiasm, representatives of several medical schools, of the National Tuberculosis Association, and other public health bodies were consulted. All approved of the plan. It was in August 1915 that Doctor Bishop announced that Mr. Samuel Mather[5] of Cleveland had pledged $5,000 a year for three years to support a school of tuberculosis, and Doctors Baldwin, Lawrason Brown, Allen K. Krause, and others immediately began organization of a course of six weeks which would, in the words of Baldwin (5), "give opportunities for laboratory study and clinical study, which will stimulate interest and maintain a more scientific atmosphere in the work of the various sanatoria, and in general aid the anti-tuberculosis campaign throughout the country along the best lines of effort."

Doctor Trudeau did not live to see the culmination of these plans. He died on November 15, 1915. Among the changes which followed were those looking toward the perpetuation of the name of the great American pioneer in tuberculosis. The Sanatorium which he had founded in 1884 and which had become a focus of treatment and experimentation under the name of "The Adirondack Cottage Sanitarium" was henceforth to be known as "Trudeau Sanatorium." The memorial aspect of the Edward L. Trudeau Foundation has already been described. Now that Doctor Trudeau was gone there seemed every reason why the school which had enlisted his interest, but with which out of modesty alone he felt his name ought not to be associated, should become another memorial to him.

And thus it was that the Trudeau School of Tuberculosis began its first session of six weeks on May 17, 1916 with a class of sixteen physicians. The faculty consisted of Doctor Baldwin, who had been chosen as director of the School; Dr. Lawrason Brown; Dr. Allen K. Krause; Dr. Albert H. Garvin; Dr. Fred H. Heise; and Dr. Hugh M. Kinghorn. Visiting lecturers during the session were Professor William H. Welch of John Hopkins University; Dr. Hermann M. Biggs, New York State Health Commissioner; Dr. Theobald Smith, Director of Rockefeller Institute at Princeton, New Jersey; Dr. Vincent Y. Bowditch, Medical Director of Sharon Sanatorium, Boston, Massachusetts; Dr. Elliott P. Joslin, Assistant Professor of Medicine, Harvard University; Dr. H. R. M. Landis, Director of The Henry Phipps Institute; Dr. James Alexander Miller, Chief of Tuberculosis Clinics, New York City; Dr. Robert H. Bishop, Secretary of the Cleveland Anti-Tuberculosis League, and Dr. H. Gideon Wells, Professor of Pathology, University of Chicago. Never before had such a small band of earnest students been lectured to by such a large group of outstanding leaders in the tuberculosis world!

The success of the school was immediate and has been continuous. Enrollments have varied from sixteen to thirty-two, the maximum number which can be accepted on the plan of small group teaching which obtained from the start.

[5] Mr. Mather continued his annual gift of $5,000 for eleven years. Since 1939 the Lillia Babbitt Hyde Foundation, through the interest of its president, Mr. Charles C. Harris, has supported the School by yearly contributions of $5,000.

Oddly enough, the introduction of tuberculosis study into the curricula of medical schools and the regional courses in tuberculosis which more recently have been sponsored by the American Trudeau Society seem to have made little difference in the Trudeau School attendance. The last four sessions have had the highest average enrollment of any similar period since the school began. Dr. Edward N. Packard has been director of the Trudeau School since the death of Dr. Leroy U. Gardner in October 1946.

During the first twenty sessions the course was of six weeks' duration, but in 1935 the program was condensed and reduced to four weeks, with an optional two weeks of supplementary work at Bellevue Hospital under the auspices of Columbia University. Approximately four-fifths of each class registered for the Bellevue work. The affiliation was discontinued in 1949 by mutual arrangement of Columbia University and the Trudeau School.

Mindful of the tuberculous individual, as always, Doctor Baldwin instituted a system of scholarships by which physicians who had suffered from the disease could take the course without payment of any fee. Approximately one-third of those who have attended the school were tuberculous and most of these were granted scholarship privileges.

Doctor Baldwin remained director of the Trudeau School until 1937. Ten years later, when he died, there had been thirty-three sessions, and 767 physicians had received certificates of attendance. Graduates are working in practically every state in the Union and with one or two exceptions in every province of Canada; in Argentina, Austria, Belgium, Brazil, Bulgaria, Belgian Congo, Cuba, China, Chile, Columbia, Czechoslovakia, Costa Rica, England, Ecuador, Egypt, France, Hawaii, India, Ireland, British West Indies, Japan, Korea, Mexico, Newfoundland, Netherland West Indies, Norway, Peru, Poland, Puerto Rico, Panama, the Philippines, Paraguay, South Africa, Spain, San Salvador, Syria, and Venezuela. Many of these graduates are public health leaders or chiefs of sanatoriums in their own countries; names of those who came from Canada and the United States are to be found among the directors and officers of many tuberculosis associations, hospitals, and sanatoriums throughout the land. Some have become well-known public health workers, others are engaged in research, and still others as private practitioners have helped to cut the death rate by their skills in diagnosis and treatment. Several hold influential posts in such government departments as the Veterans Administration and in state, county, and local tuberculosis organizations.

It is not intended to convey here the idea that Doctor Baldwin's interest was confined to the Trudeau Foundation and Trudeau School from 1916 onward. From the death of the elder Trudeau, Baldwin was chairman of the executive committee of Trudeau Sanatorium, a post which became especially important with the physical growth of the institution. In 1918 he evolved, at the request of the board of trustees, a plan of expansion which was followed through the years and the execution of which fell upon his shoulders. The over-all operation of the Sanatorium came under his administration for a quarter of a century, and during these busy years he added sixty-five publications dealing with tuberculosis

to the sixty-one titles previously printed. Even after 1945, when pneumonia first enfeebled him, he maintained his interest and influence in Sanatorium and Foundation affairs, notwithstanding that six recurrent attacks progressively sapped his energies. He was able to rally his strength to meet each emergency in the institution's progress, and there were several. The sunset of his life was clouded by the deaths of Dr. Homer L. Sampson and Dr. Frederick H. Heise, key members of the Sanatorium staff, and the problem of their replacement was solved with the still strong influence of his advice. Perhaps the heaviest blow was the sudden passing of Doctor Gardner, director of the Foundation and head of the research work which had always been close to Doctor Baldwin's heart. This occurred in October 1946 at a time when Baldwin was bedridden with one of his recurrent pneumonias. Within an hour he rallied in the face of this catastrophe as he had in the others. He started in motion the machinery which immediately provided direction for carrying on the laboratory work, so there was neither interruption nor letdown. His interest was sustained until a permanent director of research was appointed in March 1947.

Doctor Baldwin's death came six weeks later when, reaching the close of a life of work such as few men have known, he passed away peacefully in his home, surrounded by his loved ones and mourned by a world-wide community of personal and professional friends. He had outlived most of his confreres with whom he labored and had come also to the end of an era in the investigation and treatment of the disease to which he had dedicated his life.

REFERENCES

(1) KRAUSE, A. K.: Editorial, Am. Rev. Tuberc., 1917, *1*, 52.
(2) HATFIELD, C. J.: Letter to the author, March 17, 1948.
(3) JAMES, W. B.: Quoted in Saranac Lake News, May 18, 1916.
(4) Society for the Study and Prevention of Tuberculosis, as quoted in New York Evening Post, February 20, 1916.
(5) BALDWIN, E. R.: Quoted in Philadelphia Public Ledger, March 19, 1916.

Biographical Data

Born Bethel, Connecticut, September 8, 1864
Son of Elijah Clark and Frances (Hutchinson) Baldwin
Yale Medical School, 1890
Intern, Hartford Hospital, Hartford, Connecticut, 1890–1891
General practice, Cromwell, Connecticut, 1891–1892
Tuberculosis specialist, Saranac Lake, 1892–1947
Married Mary Caroline Ives, June 1, 1895; one child, Henry
Assistant and later director of Saranac Laboratory, 1892–1926
President, Saranac Lake Board of Health, 1898–1901
President, Reception Hospital for Tuberculosis, 1901–1927
President, 1912–1914, Saranac Lake General Hospital; member Board of Trustees, 1912
Editor-in-chief, THE AMERICAN REVIEW OF TUBERCULOSIS 1916–1921
Member, Board of Editors, THE AMERICAN REVIEW OF TUBERCULOSIS, 1921–1946
Editor Emeritus, 1946–1947
Vice-president, Trudeau Sanatorium, 1916–1934
Chairman of Executive Committee, Trudeau Sanatorium, 1916–1947

Honorary president, Trudeau Sanatorium 1945–1947
Instituted the Trudeau School of Tuberculosis, 1916
Inaugurated (with the late Dr. Walter B. James) The Edward Livingston Trudeau Foundation, a $500,000 endowment of tuberculosis research and teaching, 1916–1917
Director, Trudeau Foundation and School, 1916–1938
Contract surgeon, Tuberculosis Consulting Examination Board, Camp Devens, 1918
Member U. S. delegation to Conference at Cannes, France, 1919, League of Red Cross Societies
President, 1910, and Emeritus member, American Climatological and Clinical Association
President, National Tuberculosis Association, 1915 and 1916
Member, Saranac Lake School Board, District 1, one year
Member of the Medical Advisory Board, United States Public Health Service, 1920
Member, Consulting Medical Board, United States Veterans Bureau, 1930–1940
Chairman, Saranac Lake Committee Boy Scouts of America, Adirondack Council, 1928–1932
Chairman, Saranac Lake Chapter, American Red Cross, 1930–1947
Member, New York State Health Commission, Tuberculosis Committee, 1931–1947
Director, Adirondack National Bank, 1935–1947
Author of more than 100 scientific papers on the subject of tuberculosis; in books the following chapters: Klebs *Tuberculosis:* "Resistance, Predisposition and Immunity," 1909; *Osler System of Medicine*, all 3 editions, "History and Etiology"; "Tuberculosis, Bacteriology, Pathology and Laboratory Diagnosis" with Doctors Petroff and Gardner, 1927
Special laboratory experimental researches on infection, immunity, and prevention of tuberculosis

Member: Franklin County, New York State, and American Medical Associations
American Climatological and Clinical Association (emeritus)
Association of American Physicians (emeritus)
National Tuberculosis Association (life)
American Association of Pathologists and Bacteriologists
American Society for Clinical Investigation (emeritus)
New York Academy of Medicine

Positions held at time of death: Honorary president, Trustee, and Chairman of the Executive Committee, Trudeau Sanatorium
Honorary president, Prescott House, formerly Reception Hospital
Chairman, Saranac Lake Chapter, American Red Cross
Trustee, General Hospital of Saranac Lake
Trustee, Saranac Laboratory
Trustee, Northwoods Sanatorium
Director, Adirondack National Bank & Trust Company
Editor emeritus, THE AMERICAN REVIEW OF TUBERCULOSIS

Honorary degrees: Master of Arts, Yale, 1914
Doctor of Science, Dartmouth, 1937
Honorary Life Member, Tuberculosis Society of Scotland
Awarded Trudeau Medal for outstanding work in tuberculosis, 1927
Awarded Kober Medal (Association of American Physicians) for outstanding work in medicine, 1936

Republican; Presbyterian
Home: 6 Church Street, Saranac Lake, N. Y.

BIBLIOGRAPHY

EDWARD R. BALDWIN

(1) The effect of peppermint inhalation on experimental tuberculosis, N. Y. M. J., 1895, *61*, 623; Abstract in Hygienische Rundschau.

(2) A chemical and experimental research on "Antiphthisin" (Klebs), M. Rec., 1895, *48*, 871.

(3) The need of an improved technique in the manufacture of Koch's "T.R." tuberculin, M. News, 1897, *71*, 257.

(4) A gift of philanthropy to science: The Saranac Laboratory for the Study of Tuberculosis, Scient. Am., March 6, 1897.

(5) Infection from the hands in pulmonary phthisis, Phila. M. J., December 3, 1898.

(6) Experimental studies on the preparation and effects of antitoxins for tuberculosis, Am. J. M. Sc., December 1898 and January 1899.

(7) A case of lymphatic leukaemia combined with pulmonary tuberculosis, Am. J. M. Sc., June 1899.

(8) The conditions of tuberculosis infection and their control, Yale M. J., March 1900.

(9) Some results of the climatic and sanitarium treatment of tuberculosis in the Adironacks, Albany Med. Ann., 1900, *21*, 213.

(10) Recent work on tuberculosis, Proc. 28th Ann. Meet., Am. Health A., October 22–26, 1900.

(11) Bacteriology in health and disease: Bacterio-therapeutics with especial reference to tuberculosis, Tr. Congress Am. Physicians and Surgeons, 1900, vol. *5*.

(12) Adirondacks, Ref. Handbook of the M. Sc., 1900.

(13) The action of proteolytic enzymes on bacterial toxines, J. Med. Research, 1901, *6*, 120.

(14) The selection of favorable cases of pulmonary tuberculosis for sanitarium treatment, Internat. Clin., 1901, *3*, 11th Series.

(15) Some newer aspects of heredity in tuberculosis and the sanatorium treatment, Yale M. J., 1902, *7*, 215.

(16) The tuberculous patient—when and to what extent shall his liberty be limited? Med. Rev. of Rev., January 1903.

(17) The rational application and value of specific treatment for tuberculosis, J. A. M. A., November 26, 1904.

(18) Chemistry of the tubercle bacillus, Cornet's (English translation) "Tuberculosis and Acute General Miliary Tuberculosis", 1904.

(19) Laboratory work: Its important relation to practical medicine, J. Outdoor Life, 1904, *1*, 29.

(20) Studies on the tuberculin reactor:

I. Effect of tuberculin in spreading the disease.

II. Effect of the removal of a tuberculous focus on the tuberculin reaction-susceptibility.

III. Is the reaction always dependent upon the presence of specific tubercles?
Tuberculin reaction without tubercles: Tubercle bacilli enclosed in capsules.
IV. Reaction from other substances than tuberculin:
Trypsin; peptone: Cinnamic acid: Succinic acid:
Atropin: Evidence of enzyme action.
V. How long after infection with tubercle bacilli does reaction susceptibility begin?
VI. What constituent of the tubercle bacillus induces reaction susceptibility in the animal?
J. Med. Research, 1904, *12*, 169–262.

(21) On the antihemolytic action of some cell and tissue constituents, J. Med. Research, 1904, *12*, 169–262.

(22) Studies on tuberculous serums and the bacteriolysis of bacillus tuberculosis: Part I. Serum reactions; Part II. Relation to immunity, J. Med. Research, 1904, *12*, 169–262.

(23) Anti-tuberculin or tuberculin-precipitin serums, J. Med. Research, 1904, *12*, 169–262.

(24) Differences in precipitins produced by tubercle bacilli, J. Med. Research, 1904, *12*, 169–262.

(25) Studies on immunity in tuberculosis: The properties of the serum of immunized rabbits, M. News, September 30, 1905.

(26) Report of the committee on the influence of climate in pulmonary tuberculosis, M. News, November 11, 1905.

(27) Studies in immunity in tuberculosis: III. Experiments with leucocytes, lymph glands and bone marrow extracts of immunized animals, Tr. 2nd Ann. Meet. Nat. Assn. for the Study and Prevention of Tuberculosis, May 16–18, 1906.

(28) Die "Aggressine" der tuberkelbacillen, Centralbl. f. Bakt., 1906, Number 24–25.

(29) The mechanism of resistance to tuberculosis, Proc. Path. Soc., Philadelphia, 1907, New Series, *9*, 7.

(30) The ophthalmo-tuberculin test: Some clinical observations, J. A. M. A., December 14, 1907.

(31) Opsonins in tuberculosis, Tr. A. Am. Physicians, 1907.

(32) The ophthalmo-tuberculin test, Am. J. Pub. Hyg., February 1908., Ann. Gynaec. & Pediat., 1908, *21*, 154.

(33) Review of theoretical considerations and experimental work relative to opsonins with observations at the Saranac Laboratory, New York M. J., June 27, 1908.

(34) Conclusions from 1,087 conjunctival tests by a uniform method, Reports of the Sixth International Congress on Tuberculosis, 1908, *1*, 487; J. A. M. A., 1909, *52*, 603.

(35) History and etiology of tuberculosis, Chapter 3 in Osler's *Modern Medicine*, 1908.

(36) The problem of immunity in tuberculosis, Reports of the Sixth International Congress on Tuberculosis, 1908; Am. J. M. Sc., January, 1909.
(37) Hypersusceptibility to tuberculin in tuberculosis: Its physiological and clinical importance, Yale M. J., February 1909.
(38) Resistance, predisposition and immunity (22 pp.).
(39) Individual prophylaxis (17 pp.). Chapters in Klebs' *Tuberculosis*, 1909.
(40) Progress and changes in the treatment of tuberculosis during the past twenty years, Monthly Cyclopedia and M. Bull., July 1909; Tr. Am. Climat. A., 1909, *25*, 393.
(41) General principles of tuberculin diagnosis and treatment, J. A. M. A., 1910, *54*, 260.
(42) Studies in immunity to tuberculosis: Hypersusceptibility or anaphylaxis, J. Med. Research, 1910, *22*, 189.
(43) Studies in immunity to tuberculosis: Further notes on differences in precipitins produced by tubercle bacilli, J. Med. Research, 1910, *22*, 293.
(44) Studies in immunity to tuberculosis: A contribution to the question of cattle immunization and the transformation of the human into the bovine type of tubercle bacillus, J. Med. Research, 1910, *22*, 301.
(45) President's Address: The organization of health resorts with especial reference to tuberculosis, Tr. Am. Climat. A., 1910.
(46) Dr. Trudeau's visible monument: The Adirondack Cottage Sanitarium, J. Outdoor Life, June 1910, *7*, 165.
(47) Investigations into the nature of tuberculin sensitiveness, Tr. Nat. A. for the Study and Prevention of Tuberculosis, 1911, vol. 7.
(48) Predisposition to tuberculosis and how to combat the tendency, Bulletin 4, Y. M. C. A. Health League, 1911.
(49) Specifics for tuberculosis: A review of specific methods of treatment, J. Outdoor Life, 1912, *9*, 54 (Anon.).
(50) Dr. Albert Henry Allen: An appreciation, The Parish Record (Saranac Lake), April 4, 1912.
(51) Things that visitors to health resorts should know about tuberculosis, Pamphlet No. 2, issued by the Saranac Lake Society for the Control of Tuberculosis, 1911.
(52) Allergy and re-infection in tuberculosis, Bull. Johns Hopkins Hosp., 1913, *24*, No. 269.
(53) Some new biological relations between tubercle bacilli and other acid-fast forms, Tr. Ninth Ann. Meet., Nat. A. for the Study and Prevention of Tuberculosis, 1913.
(54) Tuberculin treatment, New York State J. Med., October 1913.
(55) Experimental studies on the blood serum of cows immunized against tuberculosis. "Sensitization" of living tubercle bacilli, Arch. Internat. Med., 1914, *13*, 682.
(56) Tuberculosis: Its cause, prevention and treatment, Bull. A. M. A. press, 1914.
(57) Immunity in tuberculosis with special reference to racial and clinical manifestations, The Harvey Lectures, Series X, 1914–1915, 155.

(58) An address delivered on the occasion of the second commencement of the D. Ogden Mills School for Nurses, June 15, 1915.
(59) The difficult social position of tuberculous individuals (abstract), Mt. McGregor Optimist, 1916.
(60) The Trudeau School of Tuberculosis, J. Outdoor Life, February, 1916.
(61) Therapy as related to immunology in tuberculosis, New York M. J., March 18, 1916.
(62) Address of the President: Tr. Twelfth and Thirteenth Ann. Meet., Nat. A. for the Study and Prevention of Tuberculosis, 1916 and 1917.
(63) The consumptive and his neighbors, The Survey, July 22, 1916.
(64) The advantages of special training in tuberculosis in sanatorium surroundings, Tr. Am. Climat. & Clin. A., 1916.
(65) Latent tuberculosis: Its importance in military preparation, Cleveland M. J., June 1917.
(66) Research problems in tuberculosis, Boston Med. & Surg. J., January 24, 1918.
(67) Tuberculin in 1917, Therapeutic Gazette, March 1918.
(68) Report of the section on tuberculosis. Medical conference held at Cannes, France, April 1 to 11, 1919 at the invitation of the Committee of Red Cross Societies. Pamphlet 7-A issued by League of Red Cross Societies, Geneva, Switzerland, 1919.
(69) Medical reminiscences: A call upon Robert Koch in his laboratory in 1902, J. Outdoor Life, October 1919.
(70) Visits to German sanatoria in 1902: Falkenstein and Ruppertshain: Reminiscences of Dettweiler, J. Outdoor Life, April 1920.
(71) Visits to German sanatoria in 1902, J. Outdoor Life, January 1920.
(72) A proposed sanatorium university (editorial), Am. Rev. Tuberc., 1920, *4*, 66.
(73) Governmental hospital facilities for discharged tuberculous soldiers, Am. Rev. Tuberc., 1920, *4*, 205.
(74) Book review: *A Study in the Epidemiology of Tuberculosis, with Special Reference to Tuberculosis of the Tropics and of the Negro Race*, Am. Rev. Tuberc., 1920, *4*, 806.
(75) Experimental arrested tuberculosis and subsequent infections, Second report. Nat. Tuberc. A. Tr., 1920, *16*, 350.
(76) Postgraduate education in tuberculosis, Nat. Tuberc. A. Tr., 1921, *17*, 198.
(77) Prevailing beliefs about infection in tuberculosis, Am. Climat. A. Tr., 1921, *37*, 142.
(78) Reinfection tuberculosis: Experimental arrested tuberculosis and subsequent infections (with Dr. L. U. Gardner), Am. Rev. Tuberc., 1921, *5*, 429.
(79) Additional or reinfection tuberculosis, Brit. J. Tuberc., 1922, *16*, 120.
(80) Changes in virulence of tubercle bacilli, New York State J. Med., 1922, *22*, 524.
(81) The etiology of tuberculosis in its modern aspects, New York Tuberc. A. Bull., vol. 3, November–December 1922.

(82) Report of medical investigation of granite cutters of Barre, Vermont, Bureau of Labor Statistics, U. S. Dept. of Labor Bull., No. 293, 1922.
(83) Laboratories for tuberculosis sanatoria or hospitals.
(84) What is tuberculosis? Michigan Out-of-Doors, 1922, pp. 6, 12.
(85) The historical development of tuberculosis prevention in America with special reference to New York State, Proc. New York State Historical Assn., 1923, p. 232.
(86) Relation of National Tuberculosis Association to medical research in tuberculosis, Am. Rev. Tuberc., 1924, *9*, 285.
(87) The need for better care and nursing for the tuberculous both in institutions and at home, Hosp. Social Service, 1925, *11*, 135.
(88) Successive stages in control of tuberculosis, Canad. M. A. J., 1925, *15*, 693.
(89) Problem of theoretical and practical training for the tuberculosis nurse, Nat. Tuberc. A. Tr., 1926, *22*, 488.
(90) On awarding Trudeau Medal to Dr. Theobald Smith, Nat. Tuberc. A. Tr., 1927, *23*, 55.
(91) Tuberculosis and the general practitioner, New York State J. Med., 1927, *27*, 401.
(92) Absolute and relative value of laboratory procedures in diagnosis of tuberculosis, Johns Hopkins Univ. School Hyg., De Lamar Lecture, 1927, p. 99.
(93) Tuberculosis: Bacteriology, Pathology and Laboratory Diagnosis (with S. A. Petroff and Leroy U. Gardner), Lea and Febiger, Philadelphia, 1927.
(94) Tuberculous infection with especial consideration of its quantity, virulence and frequency, Boston Med. & Surg. J., 1927, *197*, 49.
(95) Specific medication in tuberculosis, with special reference to chemotherapy, Boston Med. & Surg. J., 1927, *197*, 79.
(96) On awarding Trudeau Medal to Dr. Eugene L. Opie, Nat. Tuberc. A. Tr., 1929, *25*, 13.
(97) Historical review: The pathology of tuberculosis, Nat. Tuberc. A. Tr., 1929, *25*, 149.
(98) Danger of tuberculous infection in hospitals and sanatoria, U. S. Vet. Bureau M. Bull., 1930, *6*, 1.
(99) Review of progress of control of tuberculosis and advances in its pathology and bacteriology, New York State J. Med., 1931, *31*, 195.
(100) Inadequacy of vaccination against tuberculosis, New York State J. Med., February 15, 1931.
(101) Züchtung eines Tuberkelbazillusstammes (typus humanus) während eines Zeitraumes von 41 Jahren, Ein Beitrag zur Geschichte de Virulenzfrage, Ztschr. f. Tuberk., 1932, *64*, 42.
(102) The semi-centennial of the tubercle bacillus, J. Outdoor Life, March 1932.
(103) Reminiscences of tuberculosis treatment, before surgical methods came into use, Stony Wold Sun Dial, January 1933.

(104) Trudeau and his laboratory, J. Outdoor Life, 1934, *31*, 455.
(105) Tuberculin: Its preparation and use in treatment and diagnosis of tuberculosis (with Leroy U. Gardner), M. Bull. Veterans Administration, 1934, *10*, 265.
(106) Effect of irradiated milk compared with vitamin D oils in inhalation tuberculosis of guinea pigs (with W. J. Steenken, Jr.), Am. Rev. Tuberc., 1937, *35*, 656.
(107) Effect of vitamin D on growth of tubercle bacilli (with W. J. Steenken, Jr.), Proc. Soc. Exper. Biol. & Med., 1937, *37*, 348.
(108) Recollections of 1890–91 at the Hartford Hospital, Hartford Hosp. Bull., June 1940.
(109) Nonpathogenic acid-fast bacilli; case of chronic pneumonitis associated with nonpathogenic acid-fast bacillus; presence of acid-fast soil bacteria on raw fruits and vegetables, Am. Rev. Tuberc., 1942, *45*, 756.
(110) History of tuberculosis research in America, Yale J. Biol. & Med., 1943, *15*, 301.
(111) Fred Henry Heise, 1883–1946 (obituary), Am. Rev. Tuberc., 1946, *54*, 321.
(112) Leroy U. Gardner, 1888–1946 (obituary), Am. Rev. Tuberc., 1946, *54*, 585